Association between alcohol and cardiovascular disease: Mendelian randomisation analysis based on individual participant data

Supplementary Appendix

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Contents

1. Studies included in the *ADH1B* collaboration

Unless otherwise stated, all eligible individuals were included in analyses in contributing studies.

1.1 Atherosclerosis Risk In Communities Study

The Atherosclerosis Risk In Communities (ARIC) Study is a population-based prospective cohort study of cardiovascular disease sponsored by the National Heart, Lung, and Blood Institute (NHLBI). ARIC originally included 15,792 individuals aged 45-64 years at baseline (1987-89), chosen by probability sampling from four US communities. Cohort members completed four clinic examinations each spread over about three years, conducted approximately three years apart between 1987 and 1998. The data used in this study are from the first visit in 1987-1989. A detailed study protocol is available on the ARIC study website (http://www.cscc.unc.edu/aric). For this study the sample was restricted to individuals of European descent by self-report and principal component analysis using genome-wide genotypes.

1.2 Avon Longitudinal Study of Parents and Children

The Avon Longitudinal Study of Parents and Children (ALSPAC) was established to understand how genetic and environmental characteristics influence health and development in parents and children (http://www.bristol.ac.uk/alspac/researchers/resources-available).[1,2] All pregnant women resident in a defined area in the South West of England, with an expected date of delivery between 1st April 1991 and 31st December 1992, were eligible and 13 761 women (contributing 13 867 pregnancies) were recruited. These women have been followed over the last 19–22 years and have completed up to 20 questionnaires. A follow-up assessment was completed 17–18 years postnatal at which anthropometry (weight, height, waist circumference), blood pressure (from both arms, then averaged to derive SBP and DBP used in analyses), carotid intima media thickness were assessed, and a fasting blood sample taken, from which the following were assayed: total and HDL cholesterol, triglycerides, CRP, insulin and glucose. DNA has been extracted from saliva or blood samples collected at various time points. The sample used for this study included only women of self-reported white ethnic origin, or, where this information was missing, those predicted to be of European origin based on 5 ancestry-informative markers. Additionally, women of self-declared Jewish faith were excluded (n=4) because the prevalence of the rare allele is much higher in most Jewish populations. Because alcohol consumption was measured during pregnancy in ALSPAC, this cohort did not contribute towards the genetic or observational analysis for any of the alcohol phenotypes. Ten principal components variables derived from GWA panel data were available for sensitivity analyses.

1.3 British Women's Heart and Health Study

The British Women's Heart & Health Study (BWHHS) is a prospective cohort study of 4,286 women aged between 60 and 79 at baseline in 1999-2001. Participants were randomly selected from general practice registers in 23 towns across England, Wales and Scotland. The criteria for the sampling frame and clinic protocols were very similar to the 20 year follow-up of the British Regional Heart Study. Baseline measurements included biomarkers and blood samples for DNA extraction taken by research nurses as well as ascertainment of a wide range of phenotypic measures. Follow-up by postal questionnaire was undertaken in 2003, 2007 and 2010-2011. Of the 4,278 participants

who gave consent for genetic studies, 15 were defined by the examining nurse as being non-white and were excluded from further genetic analyses. Of the remaining 4,263 women, 3,800 (89%) had DNA available for genotyping. Survival status is obtained from the Data Linkage Service, Health and Social Care Information Center, London and CVD events have been prospectively studied by biennial review of primary care medical records with validation checks.

1.4 British Regional Heart Study

From 1978 to 1980, 7735 men aged 40-59 were recruited from general practices across the UK. A wide range of phenotypic measures is available for established risk markers such as lipids, blood pressure and inflammatory and haemostatic markers. Most of these measures were taken both at recruitment and re-examination, which occurred in 1998-2000 when men were aged 60-79. At this re-examination 4252 participants attended and DNA was extracted for 3945. Data on important behavioural variables such as cigarette and alcohol consumption, as well as physical activity, have been regularly collected through follow up. Well validated outcome variables including major coronary heart disease and stroke, as well as cause-specific mortality, continue to be collected from medical records 30 years after recruitment.

1.5 Caerphilly Prospective Study

The Caerphilly Prospective Study (CAPS) to examine the importance of lipids, haemostatic factors, and hormones such as testosterone, cortisol and insulin (Lichtenstein et al 1987) in the development of ischemic heart disease (IHD). The initial design attempted to contact all men aged 45 to 59 years from the town of Caerphilly and adjoining villages. 2512 subjects (response rate 89%) identified from the electoral register and general practice lists were examined between July 1979 and September 1983 (phase I). Men were initially seen at an evening clinic, where they completed a questionnaire, had anthropometric measures and an ECG taken. They also completed a food frequency questionnaire at home. They subsequently re-attended an early morning clinic to have fasting blood samples for a wide variety of tests. Quality control was examined by the use of both "blind" split samples as well as a second repeat measure on a random sub-sample to examine intra-individual variation.

1.6 Cardiovascular Health Study

The Cardiovascular Health Study (CHS) is a population-based cohort study of risk factors for cardiovascular disease in adults 65 years of age or older conducted across four field centres. The original predominantly white cohort of 5,201 persons was recruited in 1989-1990 from random samples of the Medicare eligibility lists and an additional 687 African-Americans were enrolled in 1992-93 for a total sample of 5,888. The sample was restricted to individuals of European descent by self-report and principal component analysis using genome-wide genotypes.

1.7 Cleveland Family Study

The Cleveland Family Study (CFS) is the largest family-based study of sleep apnea world-wide, consisting of 2284 individuals (46% African American) from 361 families studied on up to 4 occasions over a period of 16 years. NIH renewals provided expansion of the original cohort (including increased minority recruitment) and longitudinal follow-up, with the last exam occurring in February 2006. Index probands (n=275) were recruited from 3 area hospital sleep labs if they had a confirmed diagnosis of sleep apnea and at least 2 first-degree relatives available to be studied. In the first 5 years of the study, neighbourhood

control probands (n=87) with at least 2 living relatives available for study were selected at random from a list provided by the index family and also studied. All available first degree relatives and spouses of the case and control probands also were recruited. Second-degree relatives, including half-sibs, aunts, uncles and grandparents, were also included if they lived near the first degree relatives (cases or controls), or if the family had been found to have two or more relatives with sleep apnea. Blood was sampled and DNA isolated for participants seen in the last two exam cycles (n=1447). The sample, which is enriched with individuals with sleep apnea, also contains a high prevalence of individuals with sleep apnea-related traits, including: obesity, impaired glucose tolerance, and hypertension. The sample was restricted to individuals of European descent by self-report and principal component analysis using genome-wide genotypes. In the case of related individuals, only the oldest individual in each family unit was included in the analysis.

1.8 Copenhagen City Heart Study

The Copenhagen City Heart Study (CCHS) is a prospective study of 10 388 individuals randomly selected from the population of Copenhagen, followed from blood sampling in 1991–1994 through 2007. Individuals were invited based on their Central Person Registration number, the participation rate was 55% and follow-up was 100% complete. Data on all-cause mortality were from the national Danish Civil Registration System, whereas information on cause-specific mortality was from the national Danish Causes of Death Registry.

1.9 Copenhagen General Population Study

The Copenhagen General Population Study (CGPS) is a large general population cohort study that aims to eventually recruit 100,000 participants and collect genotypic and phenotypic data of relevance to a wide range of health related problems. Individuals are randomly selected from the national Danish Civil Registration System and have to be aged 20 years or older and resident in greater Copenhagen; they also have to be white and of Danish decent. Recruitment began in 2003 and is still on-going.

1.10 Coronary Artery Risk Development in Young Adults

The Coronary Artery Risk Development in Young Adults (CARDIA) Study is a study examining the development and determinants of clinical and subclinical cardiovascular disease and its risk factors. It began in 1985 with a group of 5115 black and white men and women aged 18-30 years. The participants were selected so that there would be approximately the same number of people in subgroups of race, gender, education (high school or less and more than high school) and age (18-24 and 25-30) in each of 4 centers: Birmingham, AL; Chicago, IL; Minneapolis, MN; and Oakland, CA. These same participants were asked to participate in follow-up examinations during 1987-1988 (Year 2), 1990-1991 (Year 5), 1992-1993 (Year 7), 1995-1996 (Year 10), 2000-2001 (Year 15), 2005-2006 (Year 20), and 2010-2011 (Year 25). A majority of the group has been examined at each of the follow-up examinations (90%, 86%, 81%, 79%, 74%, 72%, and 70%, respectively). The sample was restricted to individuals of European descent by self-report and principal component analysis using genome-wide genotypes.

1.11 Cyprus Study

The Cyprus Study is a population-based cohort study of cardiovascular disease in 1106 individuals aged 40 years or more from two areas in Cyprus. Baseline data have been

collected from Pedoulas, a village in the Troodos Mountains of Cyprus their relatives who live in any one of the main towns and from a section of Nissou, a village in the Mesaoria plain 10 km south of the capital, Nicosia, between 2003-2008. These sites were randomly selected by having a blindfolded person throw darts at a map of Cyprus. All inhabitants were identified through the population list held at the Mayor's office and all those over the age of 40 years were invited to participate. This was done by setting up an open public meeting as arranged through the district's Mayor and Local Council Committee and the local Greek Orthodox Priest. The overall participation rate of those invited was 95%.

1.12 Danish Cancer and Health

The Danish Diet, Cancer, and Health (DCH) Study is a prospective cohort study with the primary aim of studying the role of diet in cancer risk but with a potential for studying other diseases as well. From December 1993 through May 1997, 80 996 men and 79 729 women aged 50 to 64 y were invited to participate in the study; 27 177 men and 29 876 women accepted the invitation. Eligible cohort members were born in Denmark, living in the Copenhagen and Aarhus areas, and had no previous cancer diagnosis in the Danish Cancer Registry. The baseline data were linked to the Danish Cancer Registry and other population-based registries, including the Danish National Registry of Patients, and the Danish Civil Registration System, using the civil registry number, which is a unique number given to everyone with an address living in Denmark since 1968. The Civil Registration System has electronic records of all changes in vital status for the Danish population since 1968, including date of death. The Danish National Registry of Patients was established in 1977, and has records for 99.4% of all discharges from non-psychiatric hospitals in Denmark. The Danish Diet, Cancer, and Health Study and the present study were approved by the Regional Ethics Committees in Copenhagen and Aarhus and by The Danish Data Protection Agency.

1.13 Edinburgh Artery Study

The Edinburgh Artery Study (EAS) is an age-stratified random sample of men and women, aged 55-74 years, which was selected between August 1987 and September 1988 from the age-sex registers of ten general practices with a geographical and socio-economical catchment population spread throughout the city of Edinburgh, UK. Subjects were excluded if they were unfit to participate (e.g. due to severe mental illness or terminal disease); excluded individuals were replaced by other randomly sampled subjects.

1.14 English Longitudinal Study of Ageing

The English Longitudinal Study of Ageing (ELSA) is a national cohort of participants (48% men) aged over 50 years recruited from the Health Surveys for England in 1998, 1999, and 2001. Genetic data were collected at wave 2 of the study (2004/5); the phenotype measurements taken at wave 2 were used for this study.

1.15 The EPIC-InterAct Case-Cohort Study

Individuals with T2D in European Prospective Investigation into Cancer and Nutrition (EPIC) cohorts between 1991 and 2007 from eight of the ten countries participating in EPIC (26 centres) were identified. Prevalent diabetes was identified on the basis of baseline self-report of a history of diabetes, doctor-diagnosed diabetes, diabetes drug use, or evidence of diabetes after baseline with a date of diagnosis earlier than the baseline recruitment date. All ascertained cases with any evidence of diabetes at baseline were excluded. Ascertainment

of incident T2D involved a review of the existing EPIC datasets at each centre using multiple sources of evidence including self-report, linkage to primary-care registers, secondary-care registers, medication use (drug registers), hospital admissions and mortality data. Information from any follow-up visit or external evidence with a date later than the baseline visit was used. To increase the specificity of the case definition, further evidence for all cases with information on incident T2D was sought from fewer than two independent sources at a minimum, which included individual medical records review in some centres. Cases in Denmark and Sweden were not ascertained by self-report, but identified via local and national diabetes and pharmaceutical registers, and hence all ascertained cases were considered to be verified. Follow-up was censored at the date of diagnosis, 31 December 2007, or the date of death, whichever occurred first.

1.16 European Prospective Investigation of Cancer: Netherlands

The European Prospective Investigation of Cancer (EPIC) study in The Netherlands is based in two centres, Bilthoven and Utrecht. The population in the two cohorts has been recruited from two regions, from the general population (Bilthoven) and from those attending for breast cancer screening (Utrecht). Recruitment was carried out between 1993 and 1997. In 2006-2007, the two Dutch cohorts have been merged into one cohort (www.epicnl.eu) to gain efficiency and sample size and to optimise the use of the data locally. The separate cohorts, however, will co-exist besides the merged cohort.

1.17 European Prospective Investigation of Cancer: Norfolk

The European Prospective Investigation of Cancer (EPIC) Norfolk is a population-based cohort study of 25,663 European men and women aged 39-79 years recruited in Norfolk, UK between 1993 and 1997. 2,100 randomly selected control subjects were chosen from a BMI study in which genome-wide genotyping data had been obtained.

1.18 European Prospective Investigation of Cancer: Potsdam

The European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam study is part of the large-scale EPIC cohort and includes 10,904 male and 16,644 female participants recruited from the general population of Potsdam and surrounding areas. The preferred age range for recruitment was 35–65 years. Baseline examination was conducted from 1994 through 1998 and included blood sampling, measurements of blood pressure and anthropometric parameters, self-administered questionnaires on diet and lifestyle, and personal computer-assisted interviews.

1.19 European Prospective Investigation of Cancer: Turin

The European Prospective Investigation of Cancer (EPIC) Turin study, part of the large-scale EPIC cohort, and includes a longitudinal cohort of 10,603 volunteers, aged 35-64 years at baseline, from the Turin area, Italy.

1.20 Framingham Heart Study

The Framingham Heart Study (FHS) began in 1948 with the recruitment of an original cohort of 5,209 men and women (mean age 44 years; 55% women). In 1971 a second generation of study participants was enrolled; this cohort consisted of 5,124 children and spouses of children of the original cohort. The mean age of the offspring cohort was 37 years; 52% were women. A third generation cohort of 4,095 children of offspring cohort participants (mean age 40 years; 53% women) was enrolled beginning in 2002. Details of study designs for the

three cohorts are summarized elsewhere. At each clinic visit, a medical history was obtained with a focus on cardiovascular content. The sample was restricted to individuals of European descent by self-report and principal component analysis using genome-wide genotypes. In the case of related individuals, only the oldest individual in each family unit was included in the analysis.

1.21-1.24 Health, Alcohol and Psychosocial factors In Eastern Europe

The multi-centre study Health, Alcohol and Psychosocial factors In Eastern Europe (HAPIEE) study assesses the health effects of dietary factors, alcohol consumption and psychosocial factors in random samples of men and women aged 45-64, selected in the Czech Republic (7 cities), Lithuania (city of Kaunas), Poland (city of Krakow), and Russia (2 districts of city of Novosibirsk). Each country was incorporated in the analysis separately.

1.25 Health In Men Study

The Health In Men Study (HIMS) arose out of a population-based randomized trial of screening for abdominal aortic aneurysms (AAAs) conducted in Perth, Western Australia in 1996–99. Only men aged 65 years and over were recruited into the trial as AAAs are uncommon below this age and are six times more common in men than women. The aim of the trial was to assess whether screening reduced mortality from AAA. Secondary outcomes included assessments of the impact of screening on all-cause mortality and quality of life and a study of the rates of expansion of screen-detected AAAs.

1.26 Health Professionals Follow-up Study

The Health Professionals Follow-up Study (HPFS) is a prospective cohort study of 51,529 US male health professionals aged 40–75 years in 1986, who completed detailed questionnaires assessing dietary intake, lifestyle factors and medical history at baseline. Follow-up questionnaires were mailed to participants every 2 years to update baseline information and to ascertain newly diagnosed disease. Participants included in this collaboration were from a nested case-control study of MI.

1.27-1.33 IMPROVE study

The IMPROVE study is a multicentre, longitudinal, observational study, which involves seven recruiting centres in five European countries: Finland, France, Italy, the Netherlands, and Sweden. Each recruiting centre was incorporated separately into the analysis. Recruitment of a total of 3598 patients (514 per centre) was targeted. Men and women, aged from 55 to 79 years, with at least three vascular risk factors, asymptomatic for cardiovascular diseases and free of any conditions that might limit longevity or IMT visualization were considered as eligible for the study. The primary objective of the IMPROVE study was to evaluate the association between C-IMT progression at 15 months and future vascular events (myocardial infarction, cardiovascular death, stroke, or any intervention in the carotid, coronary, or peripheral arterial districts occurring from the 15th to the 36th month of follow-up).

1.34 Inter99 study

The Inter99 study is a population-based randomized controlled trial, investigating the effect of lifestyle intervention (smoking cessation, increased physical activity, and healthier dietary habits) on cardiovascular disease. Data were collected with self-administered questionnaires, a physical examination, a 2 hour oral glucose tolerance test and various

blood tests. The Inter99 study population were residents in the southern part of the former Copenhagen County. An age- and sex-stratified random sample of 13,016 men and women born in 1939–40, 1944–45, 1949–50, 1954–55, 1959–60, 1964–65, and 1969–70 was drawn from the Danish Civil Registration System and invited to participate in a health examination during 1999–2001, so that they were aged 30, 35, 40, 45, 50, 55, 60, and 65 years on the day of the examination. A total of 12,934 were eligible for invitation. The baseline participation rate was 52.5% (n = 6,784).

1.35 Ischemic Stroke Genetic Study/Siblings with Ischemic Stroke Study

The Ischemic Stroke Genetic Study (ISGS) is a multicenter cohort study. Cases were recruited from inpatient stroke services at five United States academic medical centers. Cases are adult men and women over the age of 18 years diagnosed with first-ever ischemic stroke confirmed by a study neurologist on the basis of history, physical examination and CT or MR imaging of the brain. Cases had to be enrolled within 30 days of onset of stroke symptoms.

The Siblings with Ischemic Stroke Study (SWISS) is a multicenter affected sibling pair study. Probands with ischemic stroke were enrolled at 66 US medical centers and 4 Canadian medical centers. Probands are adult men and women over the age of 18 years diagnosed with ischemic stroke confirmed by a study neurologist on the basis of history, physical examination and CT or MR imaging of the brain. Probands were required to have a history of at least one living sibling with a history of stroke. For both ISGS and SWISS, samples were restricted to individuals of European descent by self-report.

1.36 Izhevsk Family study

The Izhevsk Family study is a population-based case-control study, conducted between 2003-2005 to investigate the causes of working age male mortality. The case-control study used proxy informants (usually wife or partner) to find out about the circumstances and behaviours of the deceased men. The participants contributing towards this manuscript are controls who were followed-up as a cohort.

1.37 Malmo Diet and Cancer

The Malmo Diet and Cancer (MDC) study is set in Malmö, Sweden's third largest city. The background population consisted of all men born between 1923 and 1945 and all women born between 1923 and 1950 who were living in Malmö during the screening period 1991 to 1996 (n = 74,138). This population was identified through the Swedish national population registries. The final cohort consisted of 28,098 individuals (participation rate 40.8%). The subjects were recruited through advertisements in local media and through invitation by mail. The only exclusion criteria were inadequate Swedish language skills and mental incapacity. The Ethics Committee at Lund University approved the design of the MDC study (LU 51–90). Written informed consent was obtained from the participants.

1.38 Medical Research Council 1958 Birth Cohort

The 1958 birth cohort or the National Child Development Study (NCDS) was designed to examine how developmental, lifestyle, and environmental factors act throughout the lifespan to influence current ill health, and physiological and psychological function in early middle age. Participants are survivors from an original sample of over 17 000 births, all born in England, Wales, and Scotland, during 1 week in 1958, and followed-up by parental interview

and examination at ages 7, 11, and 16 yr and by cohort member interview at 23, 33, and 42 yr. The first biomedical assessment in adulthood was conducted by a research nurse visiting the home at 44–45 yr. During childhood, cohort members were traced through schools and immigrants born in the reference week were added to the sample. The cohort is flagged for mortality and cancer registration.

1.39 Medical Research Council National Survey of Health and Development

The Medical Research Council (MRC) National Survey of Health and Development (NSHD) is an on-going prospective birth cohort study consisting of a sample of all singleton births, born to married mothers, in England, Scotland and Wales in one week in March 1946. The sample includes all births whose fathers were in non-manual or agricultural occupations and a randomly selected one in four of all others, whose fathers were in manual occupations. The original cohort comprised 2,547 women and 2,815 men who have been followed up over 20 times since their birth. The data collected to date include cognitive function, physical, lifestyle and anthropomorphic measures as well as blood analytes and other measures. Through MRC Unit funding, a particularly intensive clinical assessment, with biological sampling, blood and urine sampling and analysis, and cardiac and vascular imaging has recently been completed when the cohort were aged 60-64 years.

1.40 Multi-Ethnic Study of Atherosclerosis

The Multi-Ethnic Study of Atherosclerosis (MESA) investigation is a population-based study of 6,814 men and women age 45 to 85 years, without clinical cardiovascular disease, recruited from six United States communities (Baltimore, MD; Chicago, IL; Forsyth County, NC; Los Angeles County, CA; northern Manhattan, NY; and St. Paul, MN). The main objective of MESA is to determine the characteristics of subclinical cardiovascular disease and its progression. Sampling and recruitment procedures have been previously described in detail57. Adults with symptoms or history of medical or surgical treatment for cardiovascular disease were excluded. During the recruitment process, potential participants were asked about their race/ethnicity. Self-reported ethnicity was used to classify participants into groups. Additional individuals were derived from the MESA Family Study, an ancillary study to MESA whose goal is to identify genes contributing to the risk for cardiovascular disease, by looking at the early manifestations of atherosclerosis within families, mainly siblings. MESA Family studied siblings of index subjects from the MESA study and sib-pairs in new families ascertained through index subjects meeting MESA enrolment criteria. In a small proportion of subjects, parents of MESA index subjects participating in MESA Family were studied but only to have blood drawn for genotyping. The MESA Family cohort was recruited from the six MESA Field Centers during May 2004 - May 2007. The number of non-classic MESA family members recruited was 1,633 (950 African-Americans and 683 Hispanic-Americans) from 594 families, yielding 3,026 sib-pairs. Participants underwent the same examination as MESA participants. The sample was restricted to individuals of European descent by self-report and principal component analysis using genome-wide genotypes.

1.41 Multinational monitoring of trends and determinants in cardiovascular diseases: Czech

The Multinational monitoring of trends and determinants in cardiovascular diseases (MONICA) was established in the early 1980s in many Centres around the world to monitor trends in cardiovascular diseases, and to relate these to risk factor changes in the population over a ten year period. All suspected coronary events in the study populations were monitored continuously from mid-1980s to mid-1990s. MONICA Czech represents the component of MONICA set in Czech Republic. The cohort used for analysis continued after the official international MONICA collaboration, and is termed “Czech post-MONICA”.

1.42 National Health and Nutrition Examination Survey III

The National Health and Nutrition Examination Survey (NHANES) is an on-going series of surveys that have been conducted by the National Center for Health Statistics since the early 1960s to assess the health and nutritional status of the US civilian non-institutionalized population using a complex, stratified, multistage survey design. NHANES has been reviewed and approved by the Institutional Review Board at the National Center for Health Statistics. DNA Specimens were available for 7,159 individuals who participated in the second phase of NHANES III (1991-1994), were 12 years of age or older, and who consented to having specimens of their blood stored for future research. Household interview data provided information on age, sex, race/ethnicity, alcohol intake, smoking status, educational attainment, physical activity, and history of heart attack and diabetes. Physical examination data provided information on body mass index, waist circumference, and blood pressure. Serum samples provided information on cotinine, cholesterol, triglycerides, and glucose. Individuals who self-reported their race/ethnicity as non-Hispanic white were eligible to be included in the current analysis. Binge drinking was defined as drinking five or more drinks of alcohol on one or more days in the past year. Fasting glucose levels were available in a subset of participants (n=1108) who had fasting blood samples drawn in the morning.

1.43 Nordic Diltiazem Study

The Nordic Diltiazem intervention study (NORDIL) was started in September 1992. This trial was a prospective randomized open blinded-endpoint multicenter, parallel-group study conducted in Norway and Sweden. The study was designed to evaluate the potential preventive effects of diltiazem compared with conventional antihypertensive drug treatment. Primary endpoints were cardiovascular mortality defined as fatal acute myocardial infarction, fatal acute cerebrovascular disease (stroke), sudden death and other fatal cardiovascular disease as well as cardiovascular morbidity defined as myocardial infarction and cerebrovascular disease (stroke). Secondary endpoints are total mortality, the development or deterioration of ischemic heart disease, congestive heart failure, atrial fibrillation, transient ischemic attacks, diabetes mellitus and renal insufficiency. Male and female patients, aged 50-69, with primary hypertension were randomly allocated to therapy starting with either diltiazem (180-360 mg daily) or conventional treatment (diuretics or beta-adrenergic blockers). Add-on therapy in the conventional treatment group excluded all types of calcium antagonists. The goal of treatment was a target diastolic blood pressure of ≤90 mmHg or a 10% diastolic blood pressure reduction.

1.44 Northwick Park Heart Study II

The Northwick Park Heart Study (NPHS) II is a prospective study of 3,012 healthy middle-aged men aged 50-64 years at recruitment, sampled from nine UK general practices between 1989 and 1994. Exclusion criteria were: history of unstable angina or acute myocardial infarction, a major Q wave on the ECG, regular anti-platelet or anticoagulant therapy, cerebrovascular disease, and life-threatening malignancy.

1.45 Nurses' Health Study I

The Nurses' Health Study I (NHS), established in 1976, is a prospective cohort study of 121,701 US female registered nurses aged 30-55 years at baseline, who completed detailed questionnaires assessing diet, lifestyle and medical history. Follow-up questionnaires were mailed to participants every 2 years to update baseline information and to ascertain newly diagnosed disease. Participants included in this collaboration were from a nested case-control study of MI. The sample was restricted to individuals of European descent by self-report.

1.46 Portuguese stroke study

The Portuguese stroke study consisted of five-hundred sixty-five unrelated patients with a clinical diagnosis of ischemic stroke, who were under the age of 65 at stroke onset, recruited through Neurology and Internal Medicine Departments throughout Portugal. Stroke was defined by the presence of a new focal neurological deficit, with an acute onset and with symptoms and signs persisting for more than 24 h. The stroke was confirmed in all patients by a computed tomography scan in 97% of cases and/or magnetic resonance imaging in 25% of patients. All patients were seen, and all neuroradiology tests were reviewed by study neurologists. Trauma, tumors, infection, and other causes of neurological deficit were excluded. Data collection forms were developed for this study that included extensive clinical information such as stroke characteristics, general clinical observation, neurological symptoms and signs, complications and interventions during hospitalization, and situation at discharge. Data were also collected on relevant lifestyle aspects and previous clinical risk factors. Five-hundred seventeen unrelated healthy individuals were included in this study as a control sample population. Control individuals were verified to be free of stroke by direct interview before recruitment, but no brain imaging studies were performed. The interview also included questions on established clinical and lifestyle risk factors for stroke. All participants were adults of Portuguese Caucasian origin.

1.47 Prevention of REnal and Vascular ENd stage Disease

The Prevention of REnal and Vascular ENd stage Disease (PREVEND) study is an ongoing prospective study investigating the natural course of increased levels of urinary albumin excretion and its relation to renal and cardiovascular disease. Inhabitants 28 to 75 years of age (N=85,421) in the city of Groningen, The Netherlands, were asked to complete a short questionnaire, 47% responded, and individuals were then selected with a urinary albumin concentration of at least 10 mg/L (N= 7,768) and a randomly selected control group with a urinary albumin concentration less than 10 mg

1.48 PRrecOcious Coronary ARtery DIsease Study

The Precocious Coronary Artery Disease study (PROCARDIS) is a European consortium investigating the genetics of coronary artery disease (CAD) in German, Italian, Swedish, and British CAD patients and controls. Controls in this study had no personal history of CAD,

hypertension, or diabetes. Ascertainment criteria for PROCARDIS probands were MI or symptomatic ACS (SACS), on the assumption that the latter represents a similar pathological process according to modified World Health Organisation diagnostic criteria before the age of 66 y. Diagnosis of MI required documentation of two or more of: (a) typical ischemic chest pain, pulmonary oedema, syncope or shock; (b) development of pathological Q-waves and/or appearance or disappearance of localized ST-elevation followed by T-wave inversion in two or more standard electrocardiograph leads; (c) increase in concentration of serum enzymes consistent with MI (e.g. creatine kinase more than twice the upper limit of normal). Diagnosis of SACS required documentation of hospitalization for one of the following indications: (a) unstable angina diagnosed by typical ischemic chest pain at rest associated with reversible ST-depression in two or more standard electrocardiograph leads; (b) thrombolysis for suspected MI (as indicated by localized ST-elevation in two or more standard electrocardiograph leads) even without later development of T-wave inversion, Q-waves, or a significant enzyme rise; or (c) emergency revascularization (i.e. during same admission) following presentation with typical ischemic chest pain at rest. Probands completed questionnaires in order to recruit affected siblings with a range of CAD diagnoses at age <66 y (MI, SACS, chronic stable angina, or intervention for coronary revascularization), who were then invited to participate in the study if their diagnoses were confirmed. Parents and up to four unaffected siblings per family were recruited wherever possible to augment the recovery of linkage phase information. Informative families were recruited in Germany, Italy, Sweden, and the United Kingdom; 99.5% of the study participants reported having a white European ancestry. The protocol was approved by the Ethics Committees of the participating institutions and all participants gave written, informed consent.

1.49 Prospective Study of Pravastatin in the Elderly at Risk

The Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) trial was designed to determine whether pravastatin 40 mg/day has primary and secondary roles in reducing coronary and cerebral events in older patients with pre-existing vascular disease or who are at high risk for vascular disease and stroke. The double-blinded, randomized, controlled trial initially screened 23,770 patients, and the patient population was subsequently narrowed (due to ineligibility or refusal to participate) to 5804 patients who were then randomized to either placebo (n = 2913) or 40 mg of pravastatin (n = 2891). Patients were recruited if they had either pre-existing vascular disease (coronary, cerebral, or peripheral) or were at increased risk for vascular disease due to such factors as smoking, hypertension, or diabetes. Inclusion criteria called for men and women between the ages of 70 and 82 years with a total plasma cholesterol of 155-350 mg/dl (4-9 mmol/l) and triglyceride levels < 200 mg/dl (6 mmol/l) . Patients were excluded if they showed signs of cognitive decline, which was assessed by a Mini Mental State Examination and a series of psychometric tests. The study population was distributed evenly between those with existing vascular disease and those with qualifying risk factors. Patients were followed every 3 months for an average of 3.2 years.

1.50 Rotterdam Study

The Rotterdam Study is an on-going, prospective, population-based cohort study on determinants of a number of chronic diseases. All inhabitants of Ommoord, a district of Rotterdam in the Netherlands, who were 55 years or over, were invited to participate in this study. Of all 10275 eligible individuals, 7983 agreed to participate (78%). Written informed

consent was obtained from all participants and the Medical Ethics Committee of the Erasmus Medical Center approved the study.

1.51 Second Manifestations of Arterial disease

The Second Manifestations of ARTerial disease (SMART) study is an on-going, prospective, single-center cohort study in patients with clinically manifest vascular disease or cardiovascular risk factors. The main inclusion criteria are coronary artery disease, cardiovascular disease, peripheral arterial disease, abdominal aortic aneurysm, or any or all of the following risk factors for atherosclerosis: hyperlipidemia, diabetes mellitus (type 1 and 2), or hypertension. Patients with a terminal malignancy, patients not able to live independently (Rankin scale >3), or patients who are not sufficiently fluent in Dutch were excluded.

1.52 Thrombosis Prevention Trial

The Thrombosis Prevention Trial (TPT) was a factorial trial of low-dose aspirin and low-intensity oral anticoagulation with warfarin in men aged between 45 and 69 years. The trial was carried out in 108 general practices throughout the UK. Men were excluded if they had a current or recent history of possible peptic ulceration, a history of possible or definite MI or stroke, and other medication incompatible with trial treatment. Men in the top 20% of the risk score distribution, or in the top 25% in regions with particularly high IHD mortality rates, were considered to be at increased risk and eligible for the trial (n=10,557). Participants who decided to take part in the trial (n=5499) visited their doctor for a medical examination, including an electrocardiogram (ECG), to confirm eligibility.

1.53 Uppsala Longitudinal Study of Adult Men

Uppsala Longitudinal Study of Adult Men (ULSAM) is a longitudinal, epidemiologic study based on all available men, born between 1920 and 1924, in Uppsala County, Sweden. The men were investigated at the ages of 50, 60, 70, 77, 82 and 88 years. Full screening and official registry data are available.

1.54 Utrecht Cardiovascular Pharmacogenetics study

The Utrecht Cardiovascular PHarmacogenetics (UCP) study enrolled participants from the population-based Pharmaco-Morbidity Record Linkage System (PHARMO, www.pharmo.nl). PHARMO links drug dispensing histories from a representative sample of Dutch community pharmacies to the national registration of hospital discharges (Dutch National Medical Registry). First, patients who received a prescription for an antihypertensive drug, and/or had hypercholesterolemia (prescription for a cholesterol-lowering drug or total cholesterol >5.0mmol/l), were selected from the PHARMO database for pharmacogenetic studies on antihypertensive drugs and statins, respectively. From this cohort, a nested case–control study was designed using hospital discharge records. Patients hospitalized for MI [International Classification of Diseases 9 code 410] were included as cases if they were registered in PHARMO for at least 1 year and were older than 18 years. The index date was defined as the date of hospitalization for the first MI. Controls met the same eligibility criteria as the cases, but had not developed MI. Controls were matched with cases on age, sex, and region, and assigned the same index date. The sample was restricted to individuals of European descent by principal component analysis using genome-wide genotypes.

1.55 Whitehall II

The Whitehall II (WH2) Study recruited 10,308 participants (70% men) between 1985 and 1989 from 20 London based civil service departments. In this longitudinal study blood pressure was recorded at phase 1 (1985-1988), phase 3 (1991-1993), phase 5 (1997-1999) and phase 7 (2003-2004). DNA was stored from phase 7 from over 6,000 participants. The study participants are all highly phenotyped for cardiovascular and other ageing related health outcomes.

1.56 Women's Health Initiative

WHI is one of the largest (n = 161,808) studies of women's health ever undertaken in the U.S. There are two major components of WHI: (1) a clinical trial that enrolled and randomized 68,132 women ages 50–79 into at least one of three placebo-control clinical trials (hormone therapy, dietary modification, and supplementation with calcium and vitamin D); and (2) an observational study that enrolled 93,676 women of the same age range into a parallel prospective cohort study.

2. Supplementary Methods

2.1 Derivation of variables

2.1.1 Data handling

All non-normally distributed continuous variables, including weekly units of alcohol, were natural log transformed. In order to include individuals who declared drinking zero weekly units, a value of one was added prior to natural logarithmic transformation. For individuals on anti-hypertensive medications, 15 mmHg was added to systolic blood pressure (SBP) and 10 mmHg to diastolic blood pressure (DBP).[3] For individuals on lipid-lowering drugs, 2.096 mmol/l was added to total cholesterol and 0.461 mmol/l to triglycerides (constants derived from Whitehall II study[4] following methods described by Tobin).[3] Non-high density lipoprotein cholesterol (non-HDL-C) cholesterol was derived by subtracting HDL-C from total cholesterol. Analyses were also conducted without addition of these constants and results reported in sensitivity analyses.

Hypertension was defined as a systolic BP of ≥140mmHg and/or a diastolic BP of ≥90mmHg.

All participants with non-missing data contributed towards analysis of continuous traits as the majority of study participants were free from coronary heart disease (CHD) at recruitment. The only exception was SMART study (set in patients with established cardiovascular disease or with multiple risk factors), which only provided data for carotid intima medial thickness (C-IMT) and N-terminal fragment B-type natriuretic peptide (BNP), and results on these traits with and without SMART were highly concordant.

2.1.2 Alcohol traits

Units per week: The main alcohol trait was weekly volume of alcohol in British units (1 British unit = 7.9 grams pure ethanol or half a pint of beer, a small glass of wine or a single measure of spirits). For studies in which this variable was not already present, we either calculated weekly volume of alcohol by summing the individual components of beverage-specific drink questions, or by converting alcohol recorded in grams/week into British units.

Binge drinking: we defined binge drinking as consumption of five or more drinks in a single occasion in the past month, or the closest possible definition to this. Please refer to **Table S2** for specific information per study.

Self-reported abstainer: definitions of self-reported abstainer varied between studies from lifelong abstention to individuals who had been abstainers for the past six months (see **Table S2** for details of definition by study).

Top-tertile of alcohol intake: in each study, we generated tertiles of alcohol consumption based on units/week. This was conducted separately for men and women.

We recorded whether the original alcohol questions referred to beverage-specific consumption (i.e. consumption questions asked separately for beer, wine and spirits rather than all beverages combined). If this was the case, the study was labelled “specific” in relation to the subgroup analysis by alcohol questionnaire, otherwise the study was labelled “not specific”. We used this information to perform a subgroup analysis according to the type of questionnaire used in each study.

2.2 Observational analyses

All continuous traits were standardized prior to this component of the analysis. To assess the shape of the association between log weekly alcohol units and each trait, in a total of 28 studies (131,490 individuals), we conducted statistical models using individual participant data in each study with each trait as the dependent variable and fitted linear and quadratic terms for alcohol, adjusted for age and gender. We pooled the beta coefficients and 95%CI for the linear and quadratic terms for alcohol across the studies using fixed-effects meta-analysis. If the 95%CI of the pooled quadratic term did not include the null value, we used this as evidence to suggest a quadratic relationship was the appropriate model to reflect the association between alcohol and the trait. We then generated plots of the pooled estimates using the summary regression coefficients as a function to illustrate the shape of the observational association between alcohol and each trait across studies

2.3. Subgroup analyses

We conducted subgroup analyses of the association of the rs1229984 A-allele on traits according to pre-specified characteristics. For the subgroup analysis based on alcohol consumption, alcohol categories were organised into a logical order and were entered into a metaregression analysis for which we used the median value for each category, using the following values: light-to-moderate (>0 to <21: 6.24 units/week); heavy drinkers (≥21: 32.88 units/week). The P value for heterogeneity that we report for alcohol subgroups was derived from this meta-regression analysis. In order to investigate in further detail the association of the genetic variant on risk of CHD events in low to moderate drinkers, we split the alcohol categories further into light (>0 to <7), moderate (≥7 to <21) and heavy (≥21 units/week) and conducted the metaregression analysis using these categories.

For all other (non-alcohol) subgroup analyses, we tested for heterogeneity between strata using unordered categorical metaregression, with the “i.” prefix for the variable name in the metaregression model. All meta-regressions were conducted using the “metareg” command in Stata.

2.4. Principal components analyses

In 11 studies of over 40,000 individuals, we had access to principal components traits. In these studies, to investigate the possibility of residual confounding by population stratification, we conducted two analyses. First, we conducted univariate linear or logistic regression analyses with each cardiovascular trait and outcome as the dependent variable, and rs1229984 A-allele carrier status as the independent variable. In the second analysis, we incorporated the first three principal component traits into each of the models. We used the first three principal component traits as visual inspection of pair-wise scatter plots with further principal component traits did not reveal evidence of structure. We compared the estimates derived from the univariate and principal component- adjusted models.

2.5. Meta-analysis of rs1229984 A-allele and cardiometabolic events

For the meta-analysis of binary traits, we used counts of cases and non-cases per genotype group. We did not use continuity correction, therefore if a study contained a “0” count for any binary trait stratified by the A-allele of rs1229984, the study was excluded from the meta-analysis. A sensitivity analysis was performed with a continuity correction imputing zero

values to 0.5 and 0.1. Meta-analysis was conducted using inverse variance weighting for the fixed effects models, and DerSimonian and Laird for random effects models.

3. Supplementary Results

3.1. Observational association between alcohol intake and traits

Observational analysis revealed that with exception of lipoprotein(a), all 21 other cardiovascular biomarkers, lifestyle and social variables were associated with alcohol consumption (**Figure S3**), with most relationships being curvilinear (**Table S12**). Light-to-moderate drinkers showed the lowest levels of smoking-related traits, body mass index (BMI) and waist circumference and the highest levels of education and physical activity. With the exception of fibrinogen (that exhibited a negative linear relationship), all coagulation and inflammation biomarkers had curvilinear associations, with light-to-moderate drinkers having the lowest values and heavy drinkers having the highest values compared to non-drinkers in general. Similar curvilinear associations were observed for systolic blood pressure, B-type natriuretic peptide, fasting glucose, and carotid intima medial thickness (CIMT). Associations of alcohol consumption with lipids and apolipoproteins varied in shape and strength. Apolipoprotein B, non-HDL-C and triglycerides showed a flat relationship. In contrast, apolipoprotein A1 and HDL-C showed the strongest positive dose-response with alcohol consumption, with no evidence of a plateau, and with heavy drinkers (>50 units/week) having the highest mean values (by 0.8 SD) compared to non-drinkers (**Figure S3**).

3.2. Association of *ADH1B* with CHD using continuity correction

Use of a continuity correction to impute zero values did not alter the association of *ADH1B* rs122984 genotype with CHD. For example, imputing zero values to 0.5 or 0.1 yielded the same odds ratio of 0.90 (95% confidence interval 0.84 to 0.96), which was numerically identical to the estimate obtained from excluding studies with zero values.

4. Supplementary Figures

Figure S1. *ADH1B* rs1229984 A-allele frequency in the 56 collaborating studies, arranged by geographical region.

41 out of 56 studies (corresponding to 84% of 261,991 participants) had a proportion of A-allele carriers <10%.

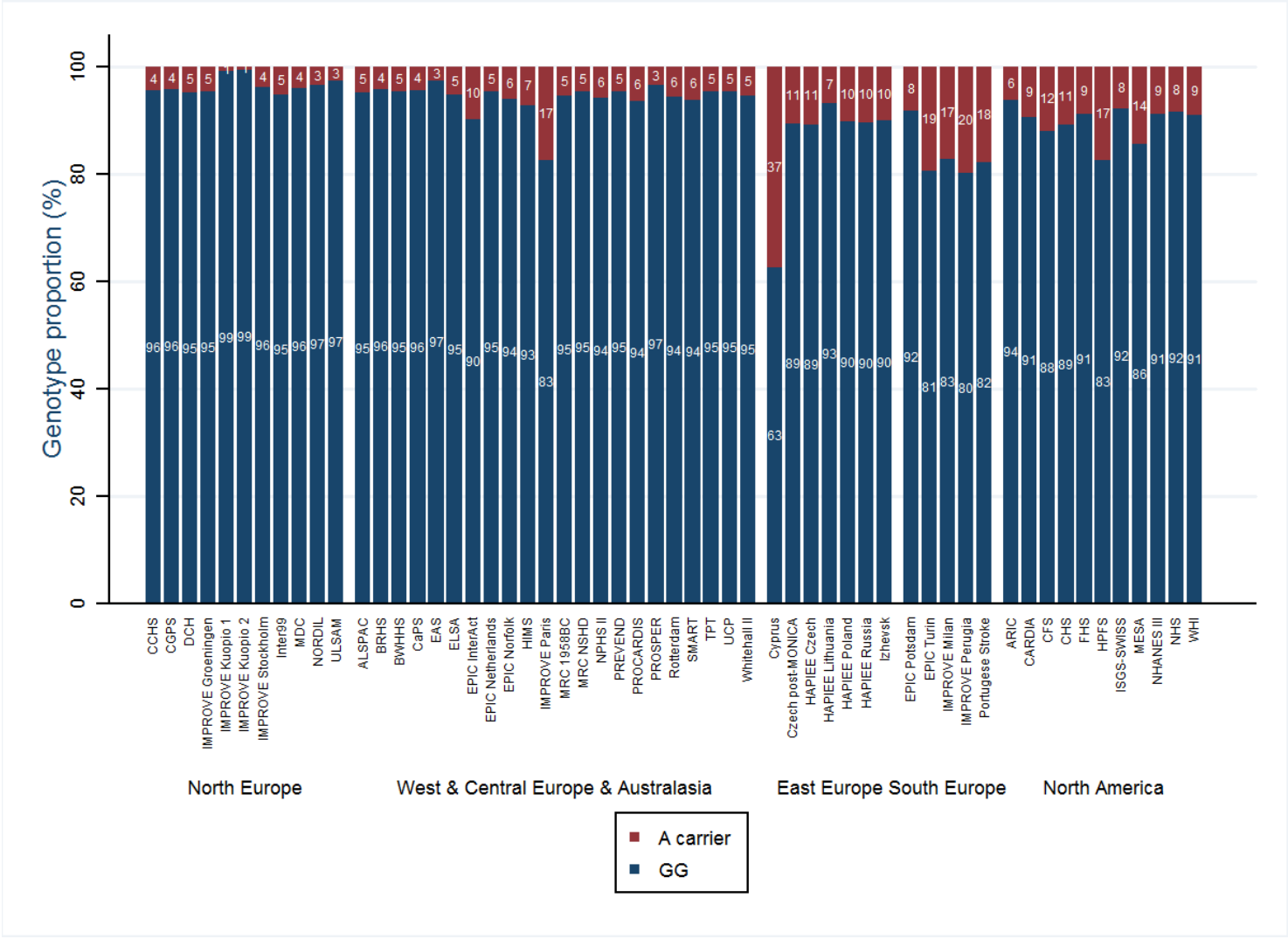
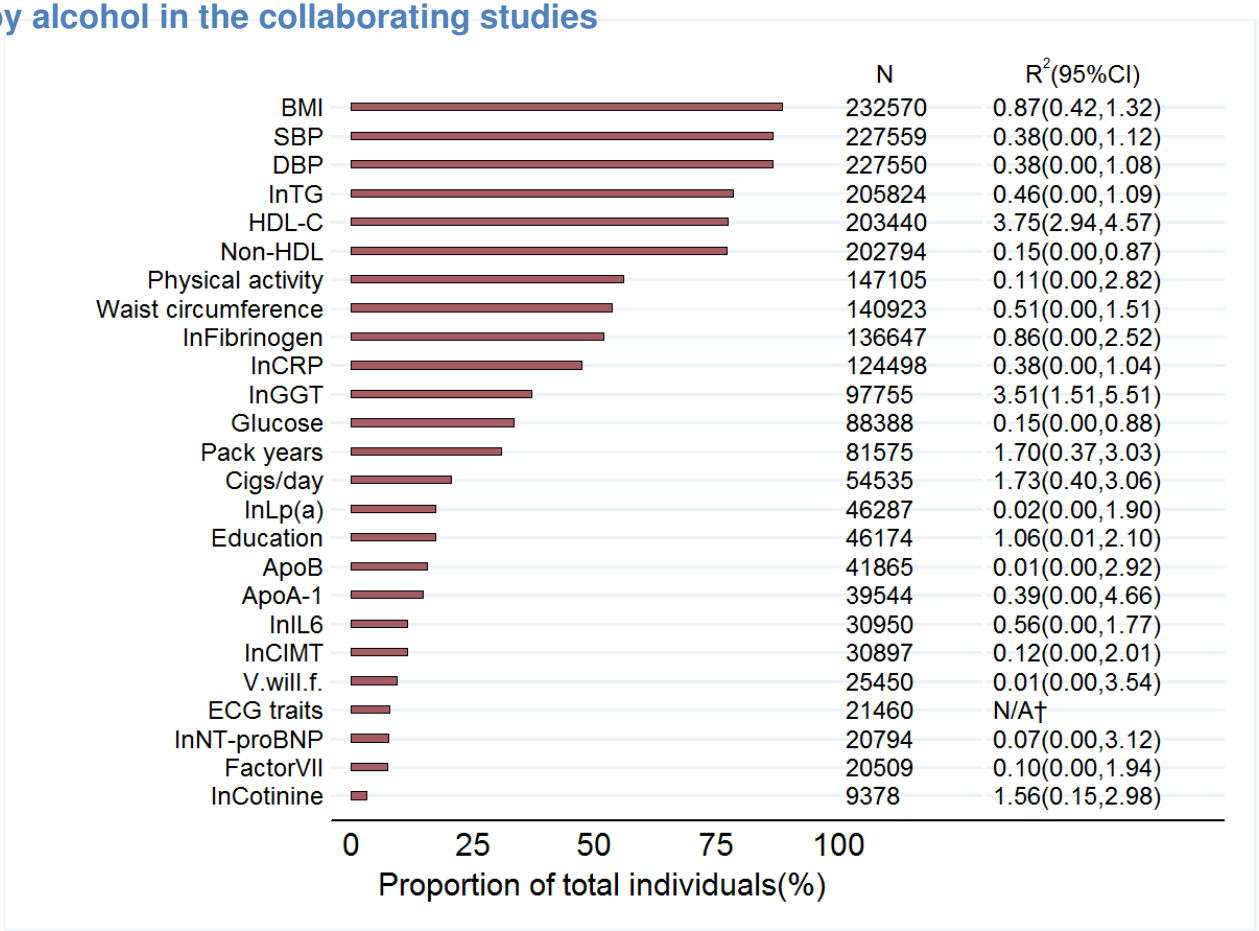


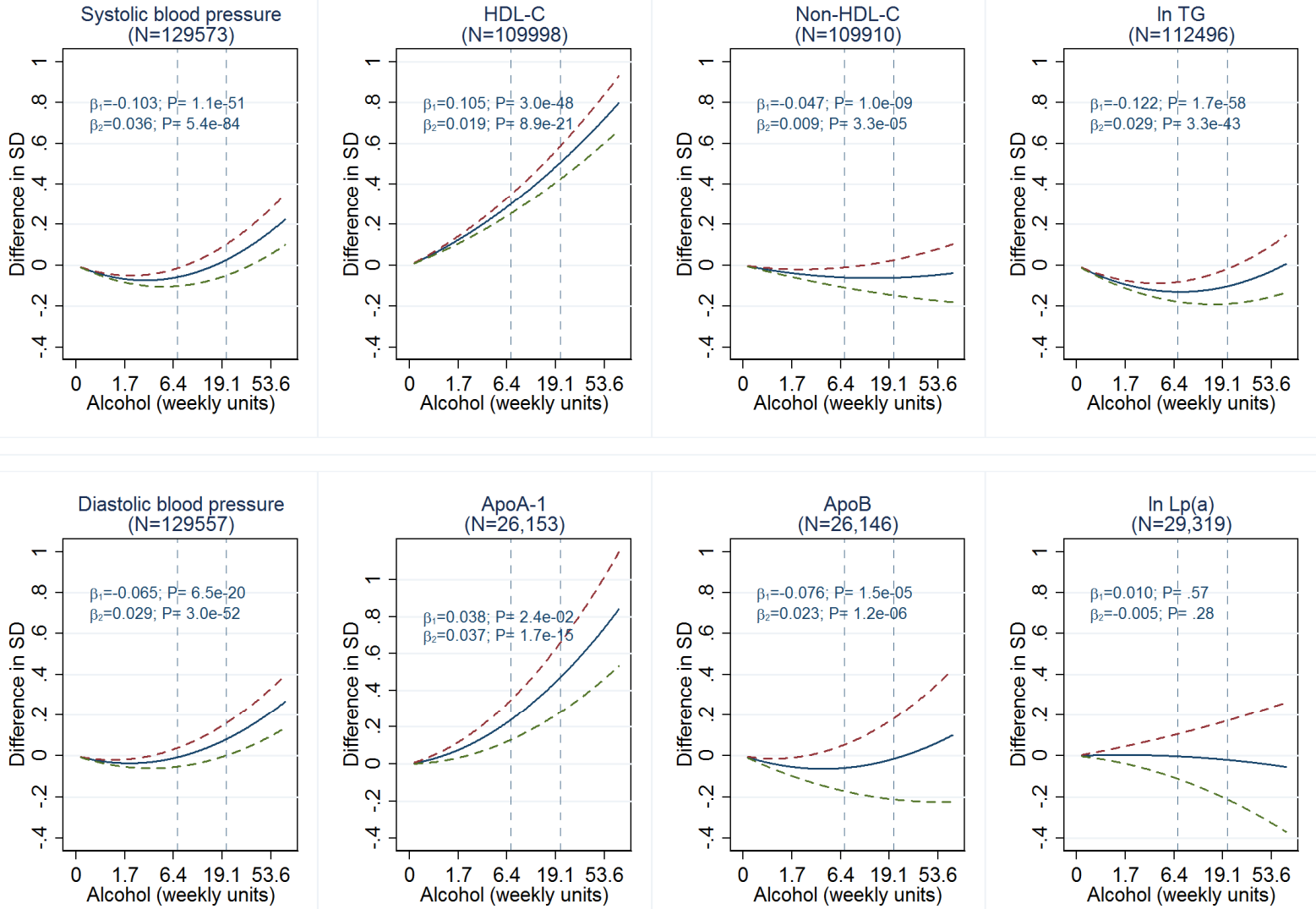
Figure S2. Total number of individuals for each trait and the proportion of variance (R^2) of each trait explained by alcohol in the collaborating studies

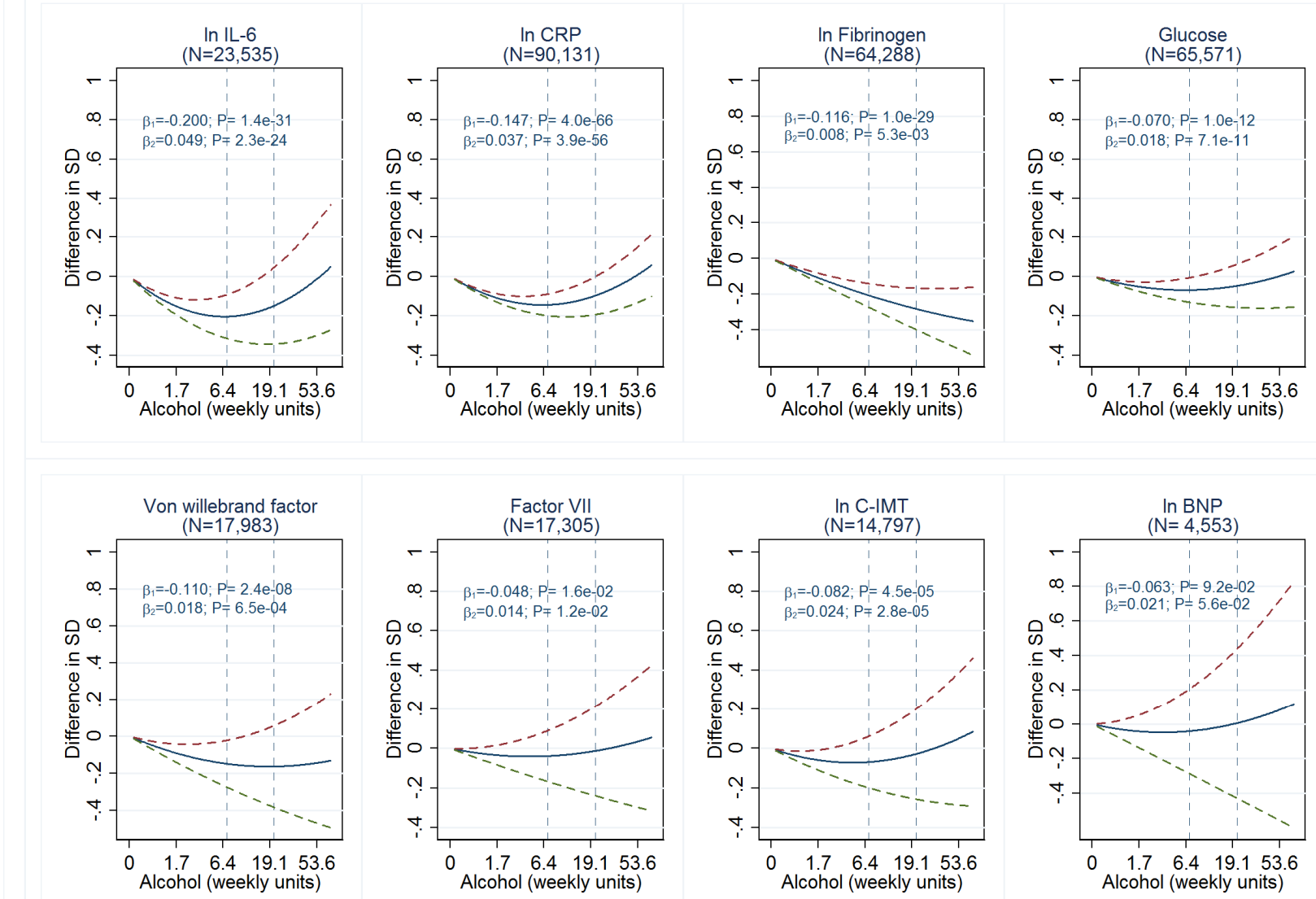


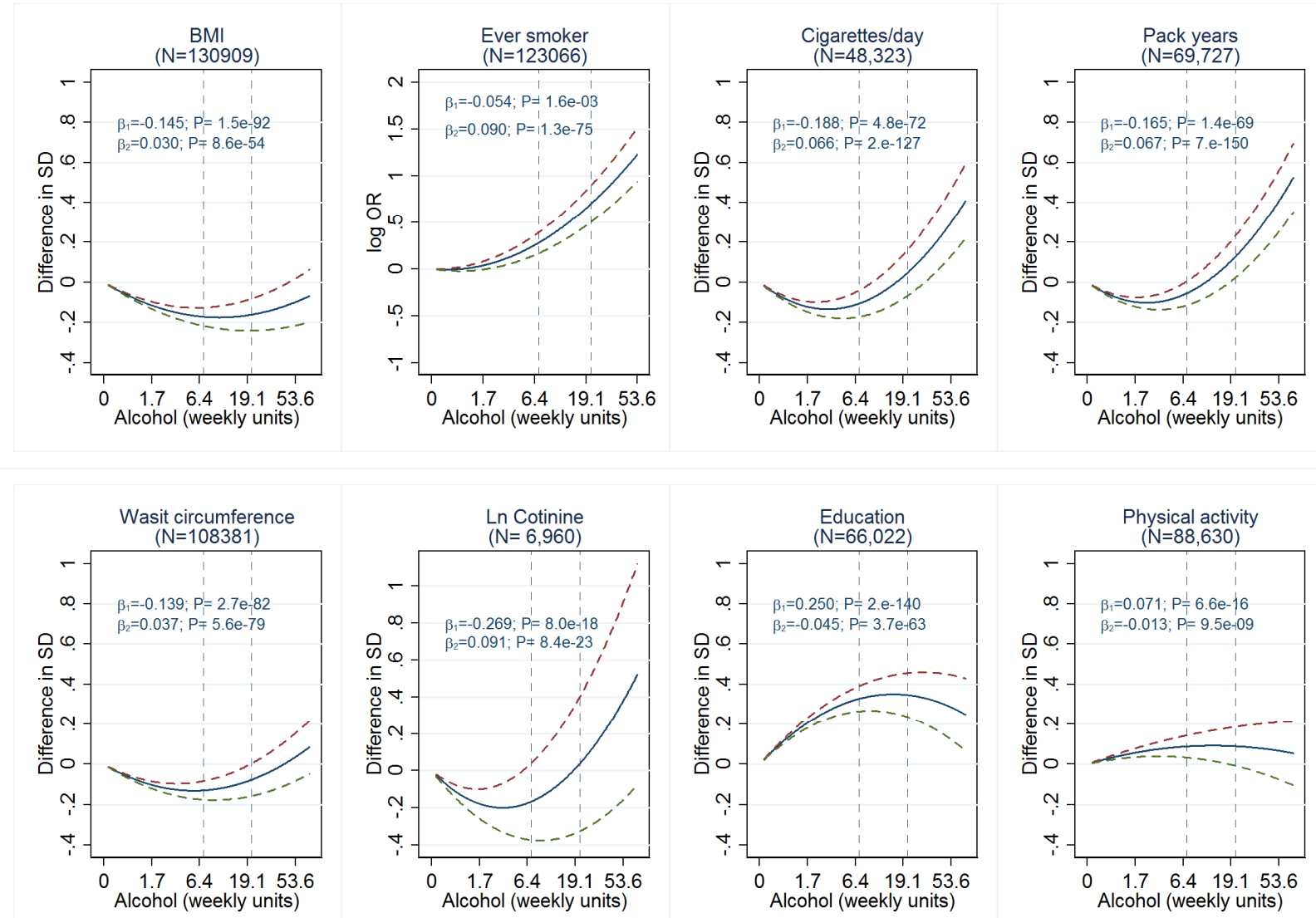
Footnote: † NA: not available as ECG estimates were obtained from look-ups and were not available in individual participant data. A lower limit of 0 was imposed on the 95%CI of the R^2 estimates, which are expressed as a percentage.

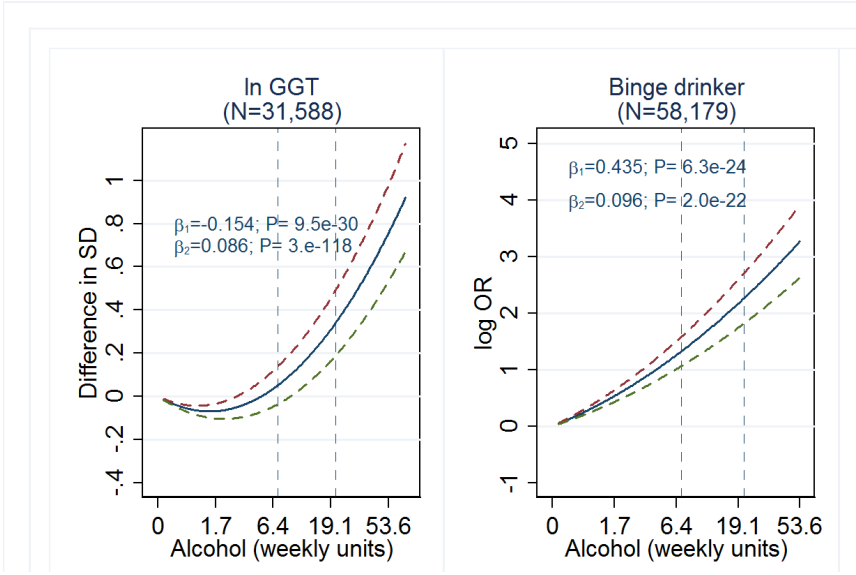
Figure S3. Observational association between alcohol intake and traits

The dose response relationship is derived from the best fit model obtained from each comparison. The values plotted represent the predicted estimates derived from the regression model that includes a linear and quadratic term for alcohol consumption (log units/week). The vertical dotted lines represent the cut-points for the main alcohol categories used in the analysis: 7 and 21 units/week.



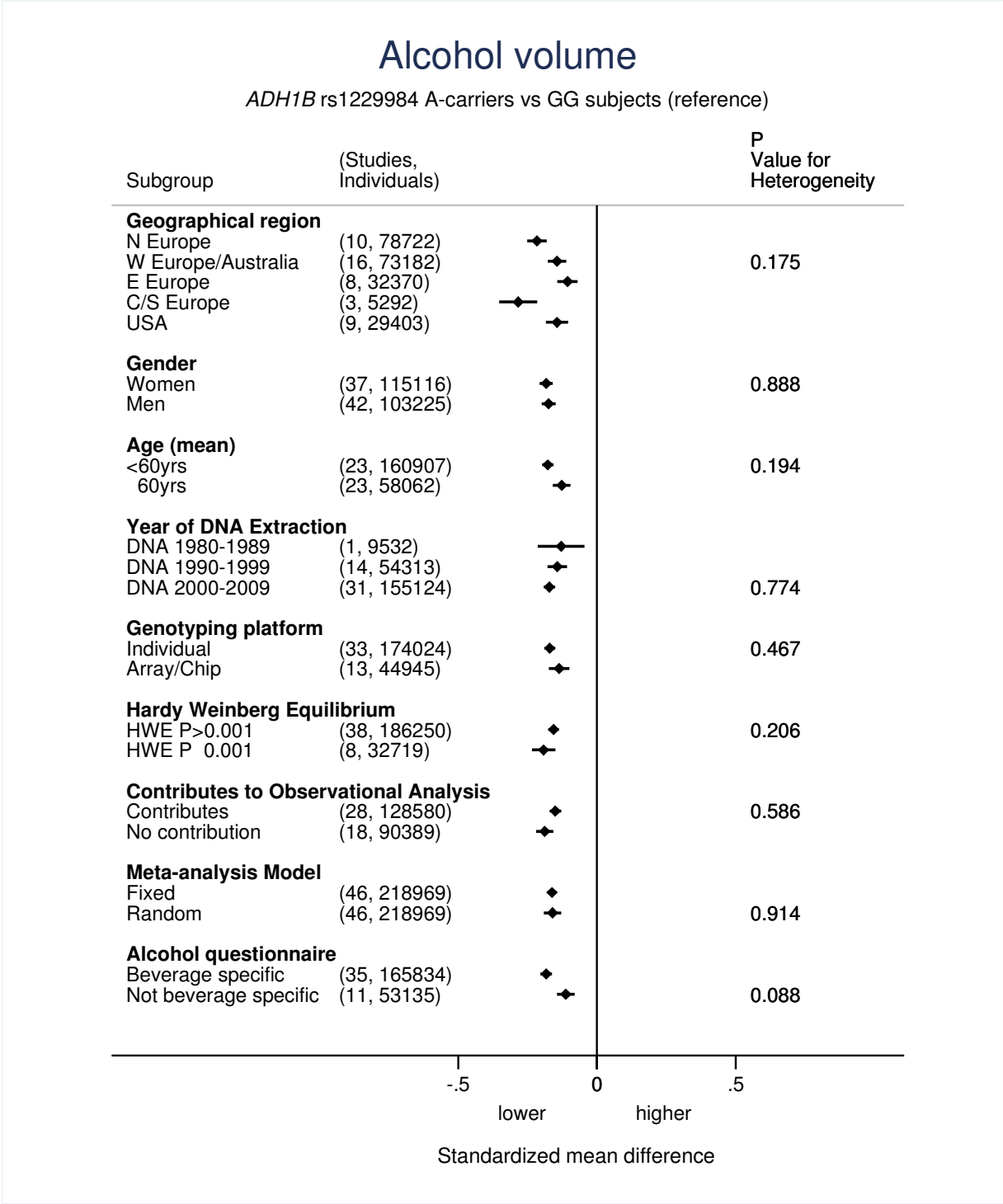

ln IL-6
(N=23,535)
β1=-0.200; P= 1.4e-31
β2=0.049; P= 2.3e-24
ln CRP
(N=90,131)
β1=-0.147; P= 4.0e-66
β2=0.037; P= 3.9e-56
ln Fibrinogen
(N=64,288)
β1=-0.116; P= 1.0e-29
β2=0.008; P= 5.3e-03
Glucose
(N=65,571)
β1=-0.070; P= 1.0e-12
β2=0.018; P= 7.1e-11
Von willebrand factor
(N=17,983)
β1=-0.110; P= 2.4e-08
β2=0.018; P= 6.5e-04
Factor VII
(N=17,305)
β1=-0.048; P= 1.6e-02
β2=0.014; P= 1.2e-02
ln C-IMT
(N=14,797)
β1=-0.082; P= 4.5e-05
β2=0.024; P= 2.8e-05
ln BNP
(N= 4,553)
β1=-0.063; P= 9.2e-02
β2=0.021; P= 5.6e-02
Difference in SD
-.4 -.2 0 .2 .4 .6 .8 1
0 1.7 6.4 19.1 53.6
Alcohol (weekly units)


BMI
(N=130909)
β1=-0.145; P= 1.5e-92
β2=0.030; P= 8.6e-54
Difference in SD
Alcohol (weekly units)
Ever smoker
(N=123066)
β1=-0.054; P= 1.6e-03
β2=0.090; P= 1.3e-75
log OR
Alcohol (weekly units)
Cigarettes/day
(N=48,323)
β1=-0.188; P= 4.8e-72
β2=0.066; P= 2.e-127
Difference in SD
Alcohol (weekly units)
Pack years
(N=69,727)
β1=-0.165; P= 1.4e-69
β2=0.067; P= 7.e-150
Difference in SD
Alcohol (weekly units)
Wasit circumference
(N=108381)
β1=-0.139; P= 2.7e-82
β2=0.037; P= 5.6e-79
Difference in SD
Alcohol (weekly units)
Ln Cotinine
(N= 6,960)
β1=-0.269; P= 8.0e-18
β2=0.091; P= 8.4e-23
Difference in SD
Alcohol (weekly units)
Education
(N=66,022)
β1=0.250; P= 2.e-140
β2=-0.045; P= 3.7e-63
Difference in SD
Alcohol (weekly units)
Physical activity
(N=88,630)
β1=0.071; P= 6.6e-16
β2=-0.013; P= 9.5e-09
Difference in SD
Alcohol (weekly units)
0 1.7 6.4 19.1 53.6



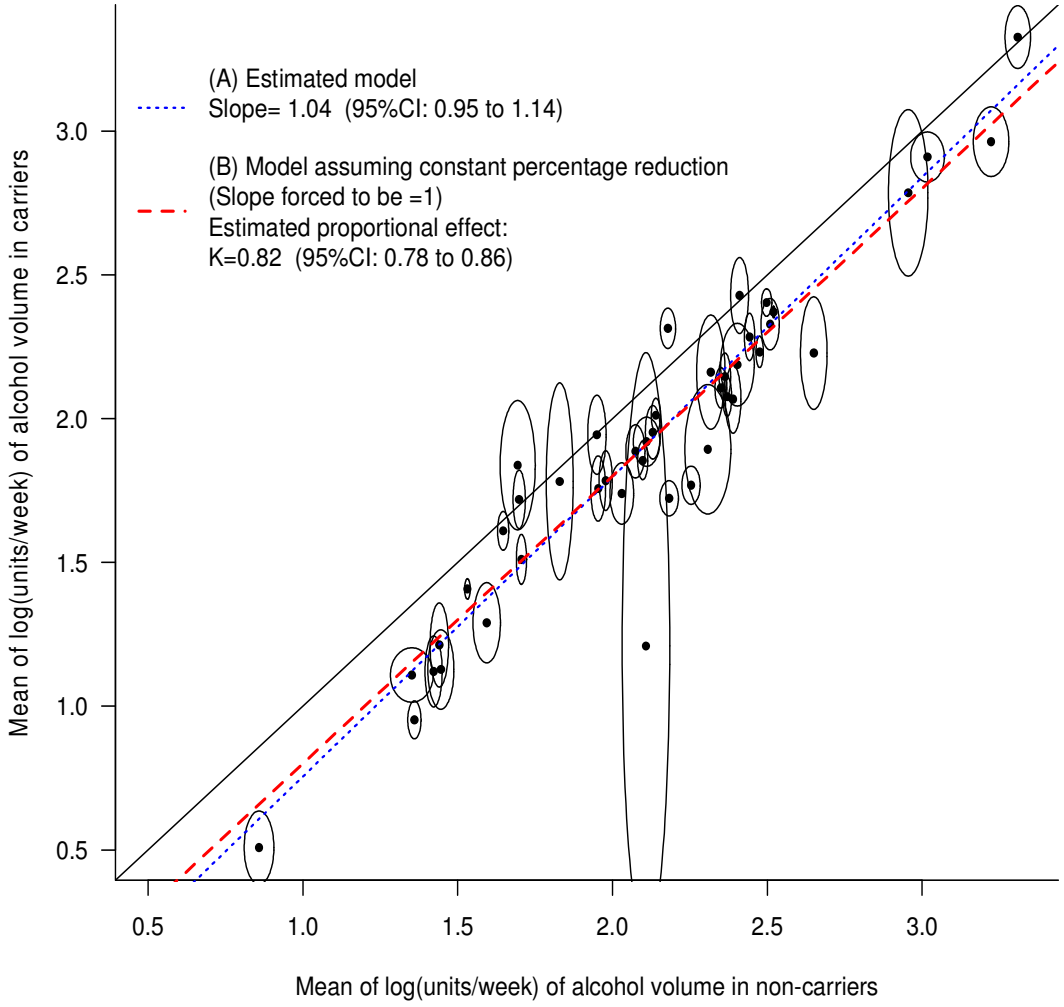
Footnotes: β_1 = linear beta coefficient β_2 = quadratic beta coefficient; both derived from meta-analyses of the fitted quadratic model, adjusted for age and gender. Alcohol units are British; to convert from British to US units, divide by 1.75 (i.e. 1 British unit=10 ml or 7.9g ethanol = 0.57 US units).

Figure S4. Subgroup analysis of the association between *ADH1B* rs1229984 (A-allele carriers vs. GG-subjects) and alcohol volume.



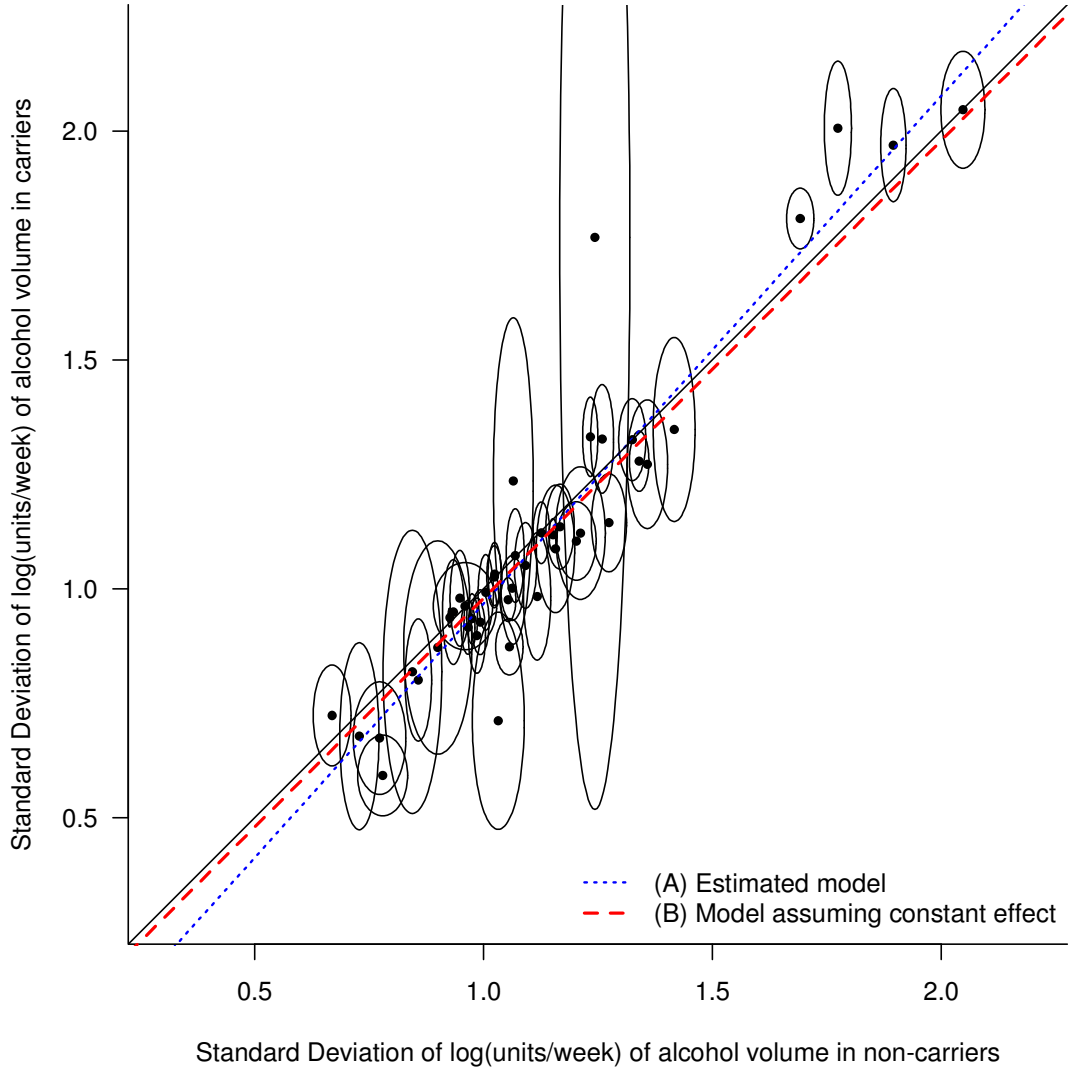
Footnote: Alcohol units are in British units; to convert from British to US units, divide by 1.75 (i.e. 1 British unit=10 ml or 7.9g ethanol = 0.57 US units).

Figure S5. L'Abbé plot of means of alcohol consumption in log(units/week) for A-allele carriers (Y-axis) and non-carriers (X-axis), among those that consume some alcohol.



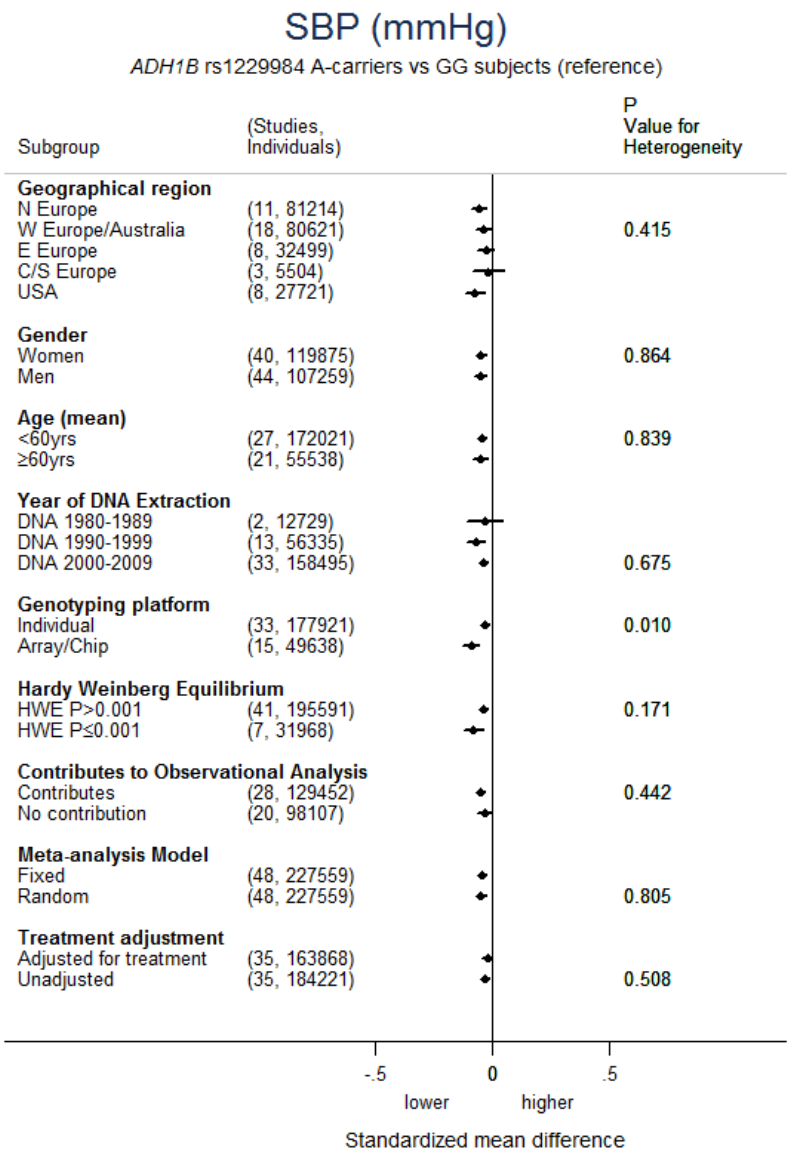
Footnote: The **blue line** represents the slope derived from the meta-regression of the mean log (units/week) of carriers against non-carriers, and its value is 1.04 (95%CI: 0.95 to 1.14) without statistical evidence to support a slope different from 1. This is compatible with the hypothesis of a constant proportional effect of the ADH1B 1229984 variant on alcohol consumption. The **red line** is derived from a model that assumes a constant effect (i.e. the slope is forced to be equal to 1). The magnitude of the constant effect is 0.82 (95%CI: 0.78, 0.86), meaning that on average ADH1B 1229984 A-allele carriers consume 18% (95%CI: 14%, 22) less alcohol volume than non-carriers, regardless of the level of alcohol consumption of the non-carries. The ellipse around the dots represents the uncertainty around the estimated means. The meta-regression lines are estimated using a Bayesian model that takes into account the uncertainties around the means as described by Thompson.[7]

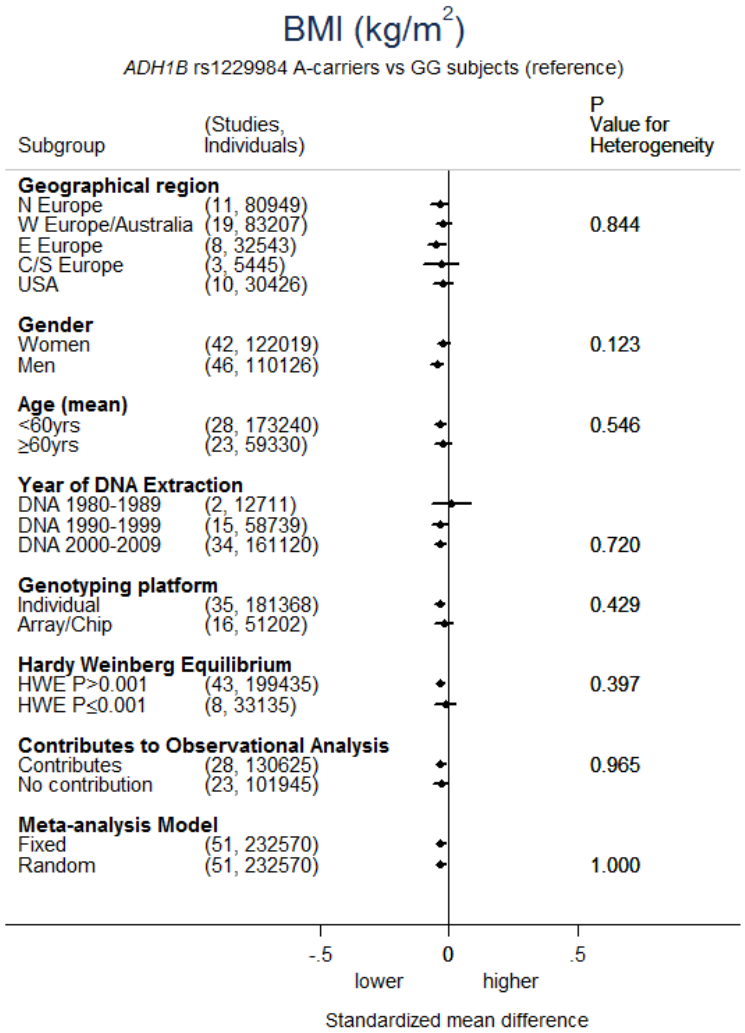
Figure S6. L'Abbé plot of the standard deviation (SD) of alcohol consumption in log(units/week) for A-allele carriers (Y-axis) and non-carriers (X-axis), among those that consume some alcohol.

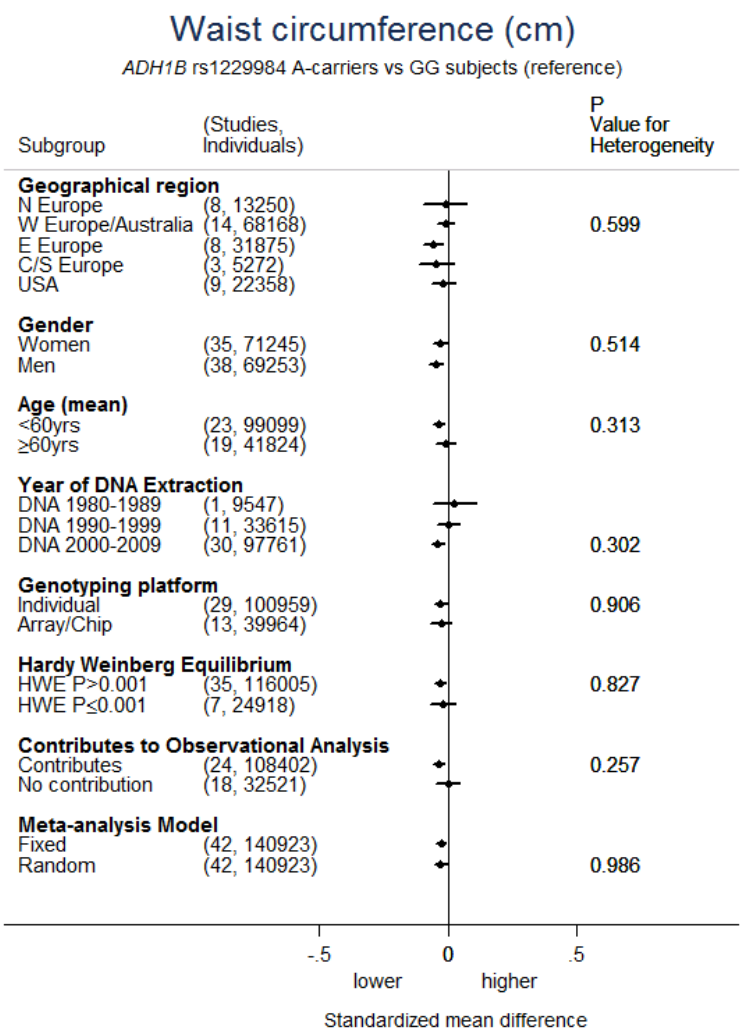


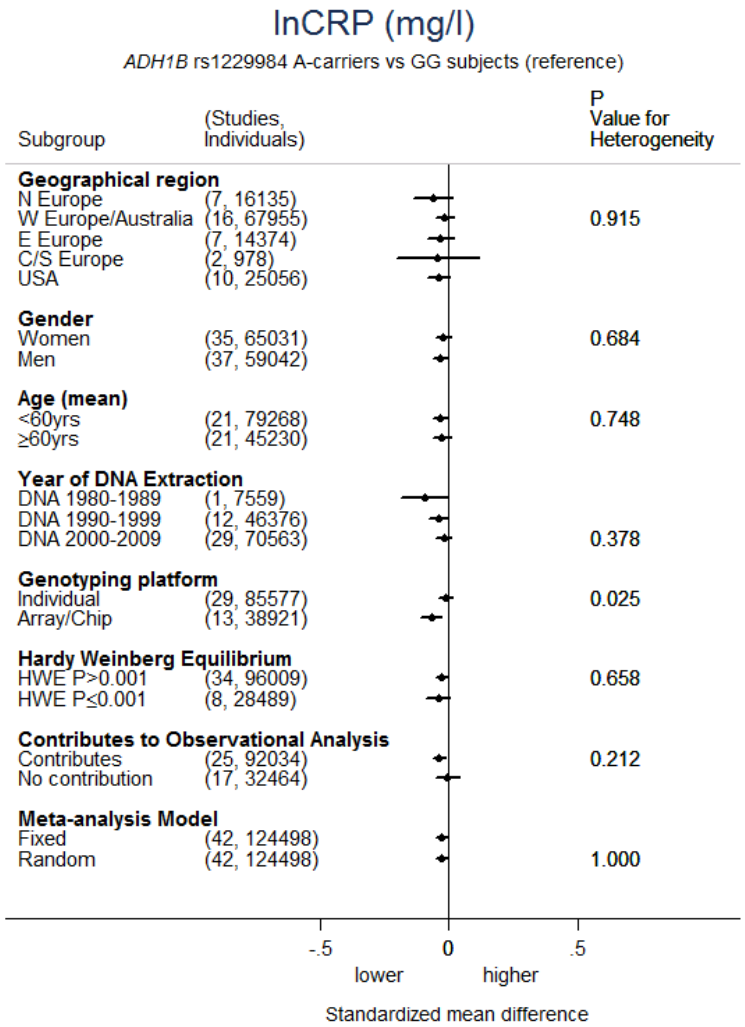
Footnote: The **blue line** represents the slope of the meta-regression of the SD in carriers against non-carriers and this overlap greatly with the black line of equality that indicates no difference in SD values between carriers and non-carriers. This overlap was even clearer when the regression line was derived from a model that assumed a constant effect (**red line**), which is supported by the observed values. The ellipse around the dots represents the uncertainty around the estimated means. The meta-regression lines are estimated using a Bayesian model that takes into account the uncertainties around the means as described by Thompson.[7]

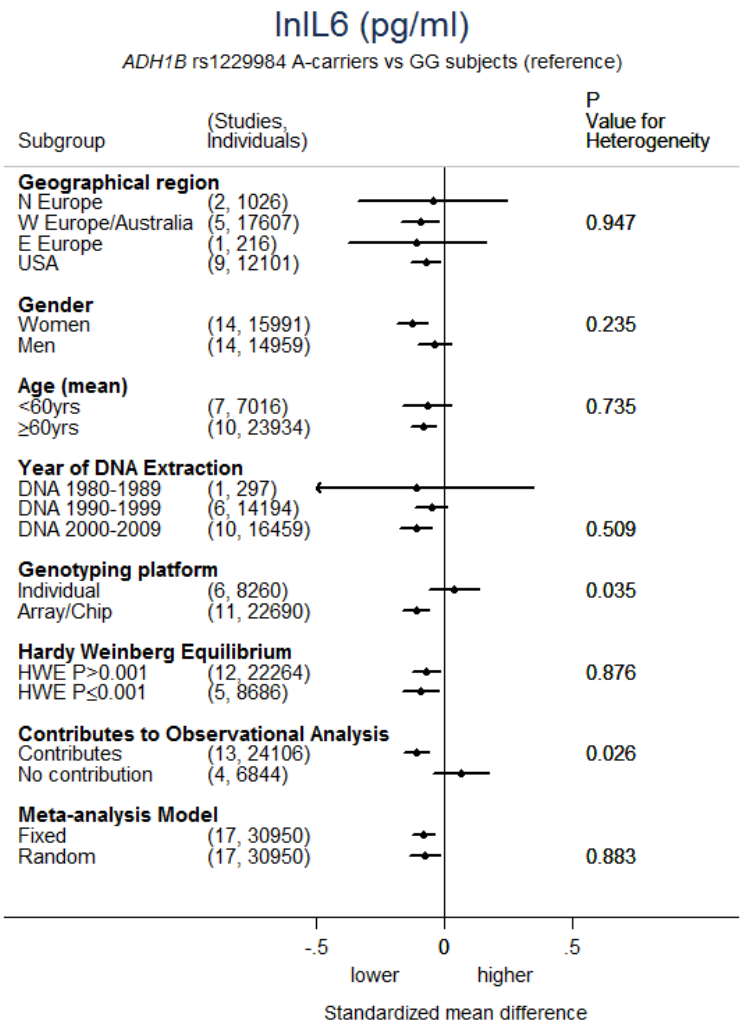
Figure S7. Subgroup analysis of the association between ADH1B rs1229984 (A-allele carriers vs. GG-subjects) and cardiovascular biomarkers showing a nominal association at P-value ≤0.05 on analysis including all individuals regardless of alcohol intake.

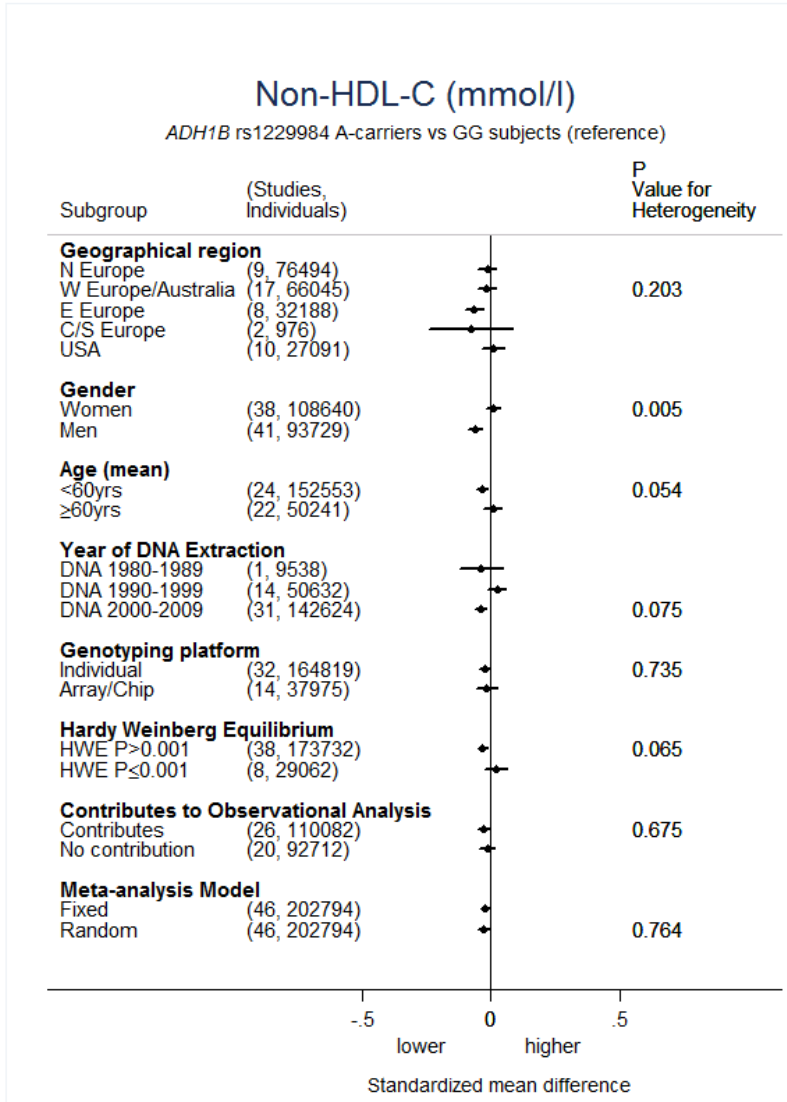



BMI (kg/m^2)
ADH1B rs1229984 A-carriers vs GG subjects (reference)
Subgroup
(Studies, Individuals)
P Value for Heterogeneity
Geographical region
N Europe (11, 80949)
W Europe/Australia (19, 83207) 0.844
E Europe (8, 32543)
C/S Europe (3, 5445)
USA (10, 30426)
Gender
Women (42, 122019) 0.123
Men (46, 110126)
Age (mean)
<60yrs (28, 173240) 0.546
≥60yrs (23, 59330)
Year of DNA Extraction
DNA 1980-1989 (2, 12711)
DNA 1990-1999 (15, 58739)
DNA 2000-2009 (34, 161120) 0.720
Genotyping platform
Individual (35, 181368) 0.429
Array/Chip (16, 51202)
Hardy Weinberg Equilibrium
HWE P>0.001 (43, 199435) 0.397
HWE P≤0.001 (8, 33135)
Contributes to Observational Analysis
Contributes (28, 130625) 0.965
No contribution (23, 101945)
Meta-analysis Model
Fixed (51, 232570)
Random (51, 232570) 1.000
-.5
0
.5
lower
higher
Standardized mean difference


Waist circumference (cm)
ADH1B rs1229984 A-carriers vs GG subjects (reference)
Subgroup
(Studies, Individuals)
P Value for Heterogeneity
Geographical region
N Europe (8, 13250)
W Europe/Australia (14, 68168) 0.599
E Europe (8, 31875)
C/S Europe (3, 5272)
USA (9, 22358)
Gender
Women (35, 71245) 0.514
Men (38, 69253)
Age (mean)
<60yrs (23, 99099) 0.313
≥60yrs (19, 41824)
Year of DNA Extraction
DNA 1980-1989 (1, 9547)
DNA 1990-1999 (11, 33615)
DNA 2000-2009 (30, 97761) 0.302
Genotyping platform
Individual (29, 100959) 0.906
Array/Chip (13, 39964)
Hardy Weinberg Equilibrium
HWE P>0.001 (35, 116005) 0.827
HWE P≤0.001 (7, 24918)
Contributes to Observational Analysis
Contributes (24, 108402) 0.257
No contribution (18, 32521)
Meta-analysis Model
Fixed (42, 140923)
Random (42, 140923) 0.986
-.5
0
.5
lower
higher
Standardized mean difference


lnCRP (mg/l)
ADH1B rs1229984 A-carriers vs GG subjects (reference)
Subgroup
(Studies, Individuals)
P Value for Heterogeneity
Geographical region
N Europe (7, 16135)
W Europe/Australia (16, 67955) 0.915
E Europe (7, 14374)
C/S Europe (2, 978)
USA (10, 25056)
Gender
Women (35, 65031) 0.684
Men (37, 59042)
Age (mean)
<60yrs (21, 79268) 0.748
≥60yrs (21, 45230)
Year of DNA Extraction
DNA 1980-1989 (1, 7559)
DNA 1990-1999 (12, 46376)
DNA 2000-2009 (29, 70563) 0.378
Genotyping platform
Individual (29, 85577) 0.025
Array/Chip (13, 38921)
Hardy Weinberg Equilibrium
HWE P>0.001 (34, 96009) 0.658
HWE P≤0.001 (8, 28489)
Contributes to Observational Analysis
Contributes (25, 92034) 0.212
No contribution (17, 32464)
Meta-analysis Model
Fixed (42, 124498)
Random (42, 124498) 1.000
-.5
0
.5
lower
higher
Standardized mean difference


lnIL6 (pg/ml)
ADH1B rs1229984 A-carriers vs GG subjects (reference)
Subgroup
(Studies, Individuals)
P Value for Heterogeneity
Geographical region
N Europe (2, 1026)
W Europe/Australia (5, 17607) 0.947
E Europe (1, 216)
USA (9, 12101)
Gender
Women (14, 15991) 0.235
Men (14, 14959)
Age (mean)
<60yrs (7, 7016) 0.735
≥60yrs (10, 23934)
Year of DNA Extraction
DNA 1980-1989 (1, 297)
DNA 1990-1999 (6, 14194)
DNA 2000-2009 (10, 16459) 0.509
Genotyping platform
Individual (6, 8260) 0.035
Array/Chip (11, 22690)
Hardy Weinberg Equilibrium
HWE P>0.001 (12, 22264) 0.876
HWE P≤0.001 (5, 8686)
Contributes to Observational Analysis
Contributes (13, 24106) 0.026
No contribution (4, 6844)
Meta-analysis Model
Fixed (17, 30950)
Random (17, 30950) 0.883
-.5
0
.5
lower
higher
Standardized mean difference


Non-HDL-C (mmol/l)
ADH1B rs1229984 A-carriers vs GG subjects (reference)
Subgroup
(Studies, Individuals)
P Value for Heterogeneity
Geographical region
N Europe (9, 76494)
W Europe/Australia (17, 66045) 0.203
E Europe (8, 32188)
C/S Europe (2, 976)
USA (10, 27091)
Gender
Women (38, 108640) 0.005
Men (41, 93729)
Age (mean)
<60yrs (24, 152553) 0.054
≥60yrs (22, 50241)
Year of DNA Extraction
DNA 1980-1989 (1, 9538)
DNA 1990-1999 (14, 50632)
DNA 2000-2009 (31, 142624) 0.075
Genotyping platform
Individual (32, 164819) 0.735
Array/Chip (14, 37975)
Hardy Weinberg Equilibrium
HWE P>0.001 (38, 173732) 0.065
HWE P≤0.001 (8, 29062)
Contributes to Observational Analysis
Contributes (26, 110082) 0.675
No contribution (20, 92712)
Meta-analysis Model
Fixed (46, 202794)
Random (46, 202794) 0.764
-.5
0
.5
lower
higher
Standardized mean difference

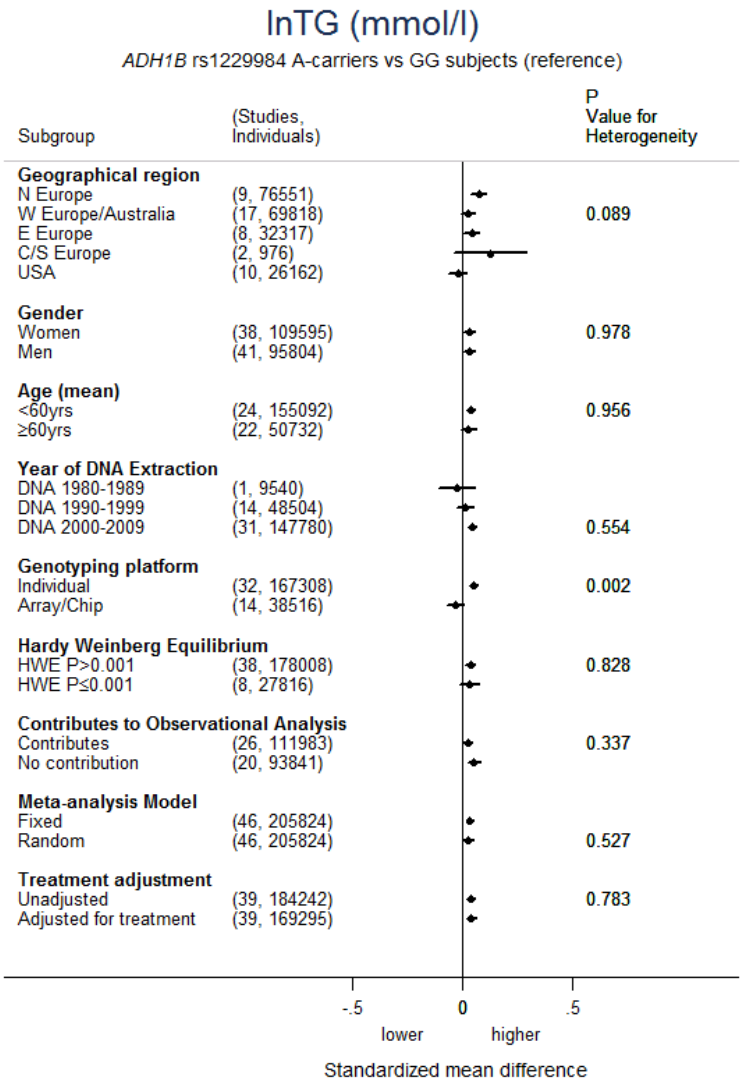

lnTG (mmol/l)
ADH1B rs1229984 A-carriers vs GG subjects (reference)
Subgroup
(Studies, Individuals)
P Value for Heterogeneity
Geographical region
N Europe (9, 76551)
W Europe/Australia (17, 69818) 0.089
E Europe (8, 32317)
C/S Europe (2, 976)
USA (10, 26162)
Gender
Women (38, 109595) 0.978
Men (41, 95804)
Age (mean)
<60yrs (24, 155092) 0.956
≥60yrs (22, 50732)
Year of DNA Extraction
DNA 1980-1989 (1, 9540)
DNA 1990-1999 (14, 48504)
DNA 2000-2009 (31, 147780) 0.554
Genotyping platform
Individual (32, 167308) 0.002
Array/Chip (14, 38516)
Hardy Weinberg Equilibrium
HWE P>0.001 (38, 178008) 0.828
HWE P≤0.001 (8, 27816)
Contributes to Observational Analysis
Contributes (26, 111983) 0.337
No contribution (20, 93841)
Meta-analysis Model
Fixed (46, 205824)
Random (46, 205824) 0.527
Treatment adjustment
Unadjusted (39, 184242) 0.783
Adjusted for treatment (39, 169295)
-.5
0
.5
lower
higher
Standardized mean difference

Figure S8. Subgroup and sensitivity analysis of the meta-analysis pooled estimate of the association between *ADH1B* rs1229984 (A-allele carriers vs. non-carriers) with HDL-C.

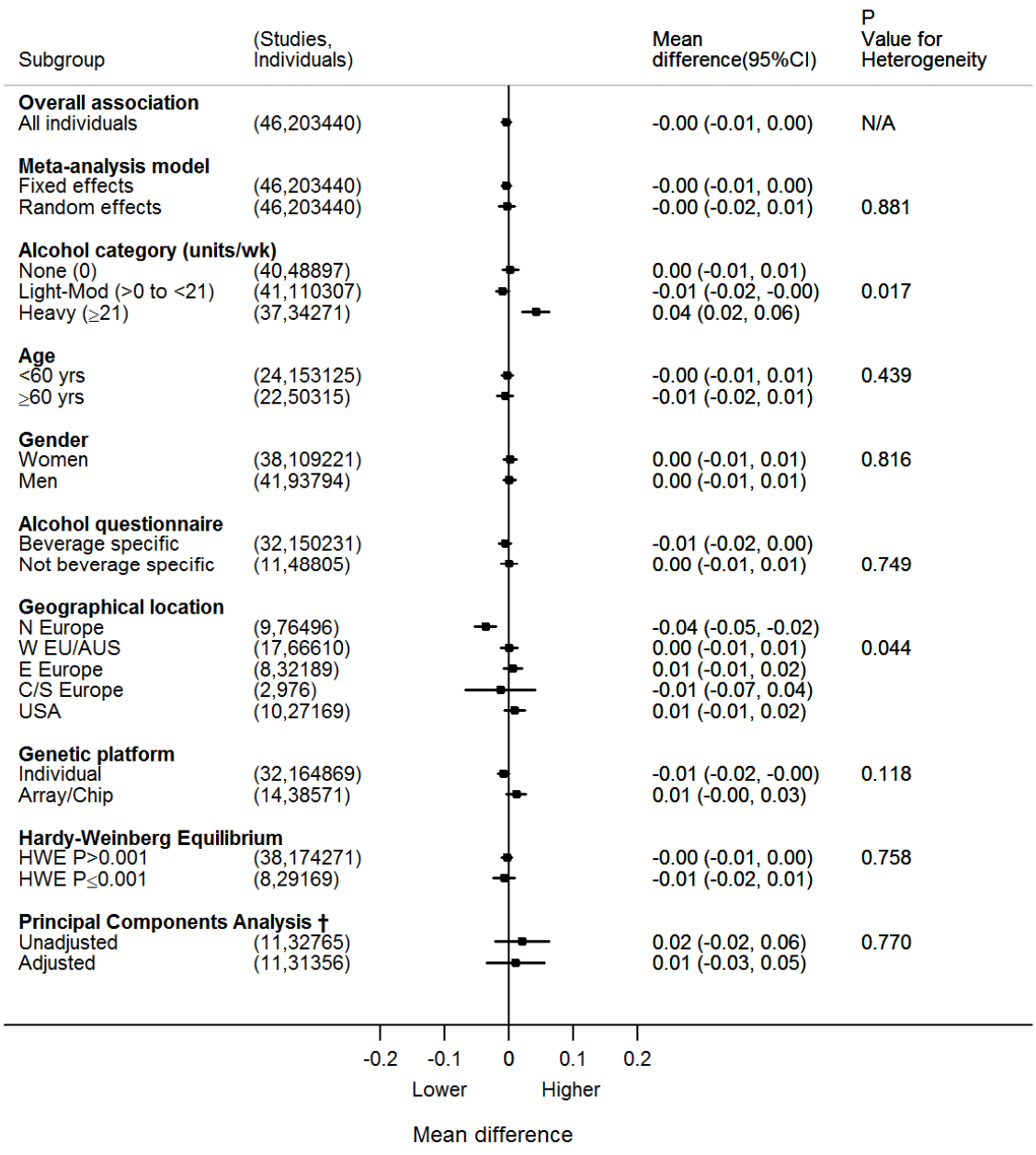
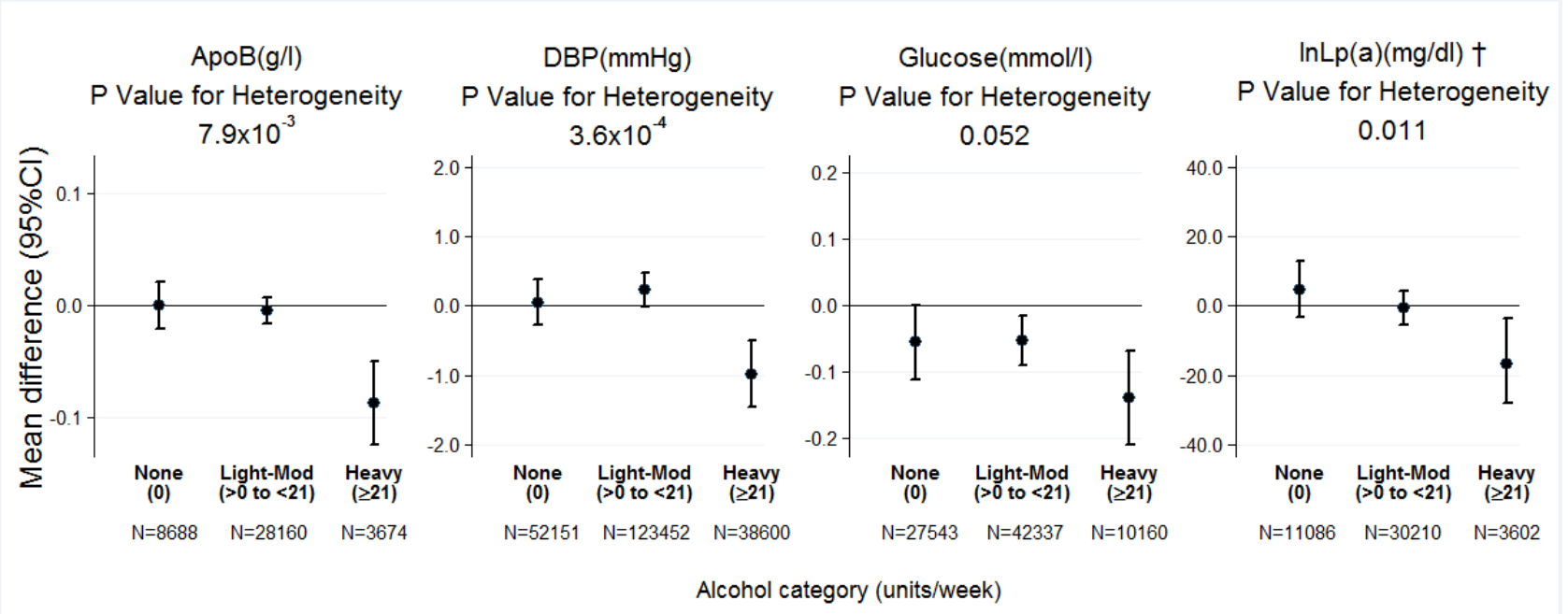
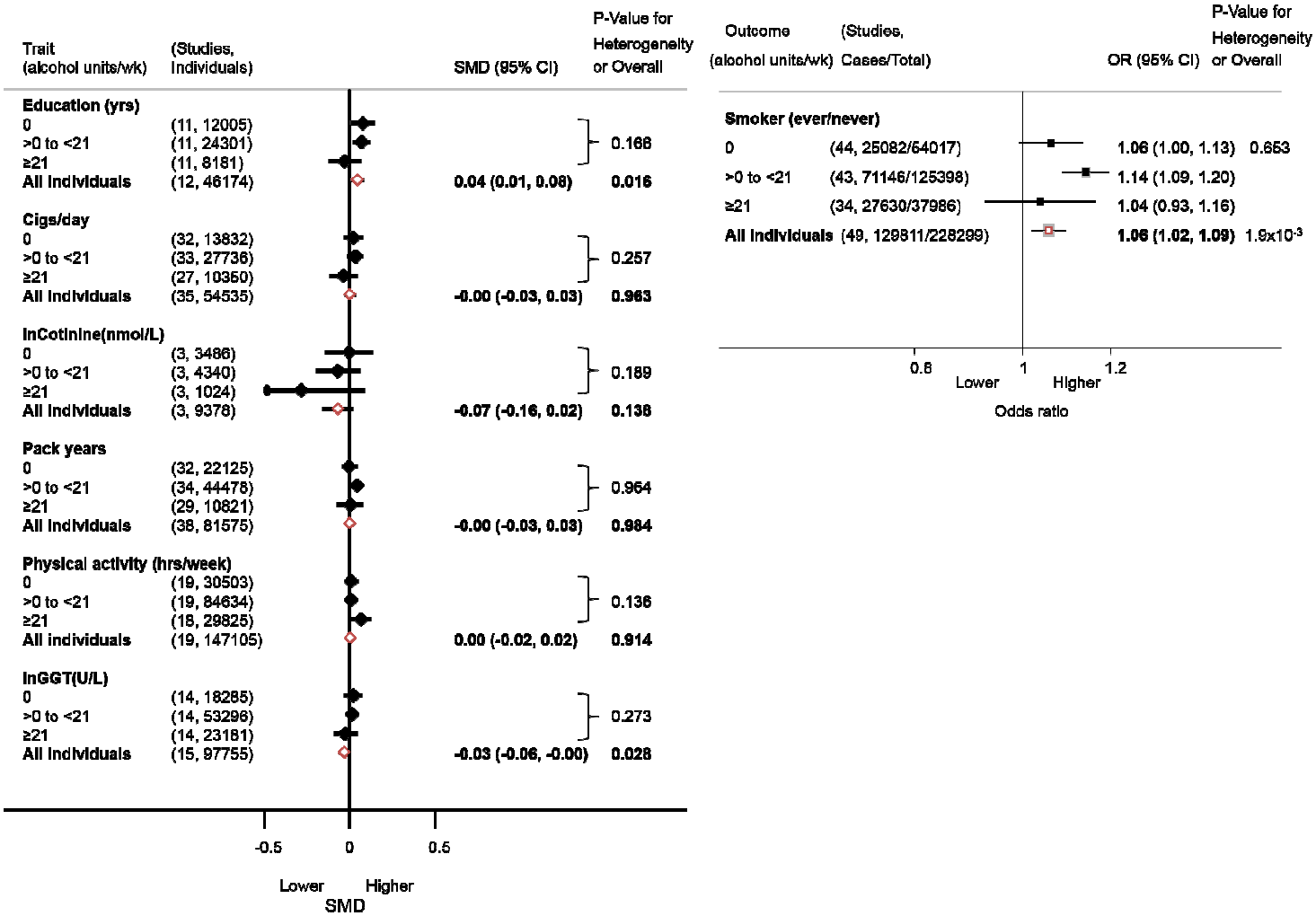


Figure S9. Meta-analysis pooled estimates of the association between *ADH1B* rs1229984 (A-allele carriers vs. GG-subjects) and cardiovascular biomarkers for traits that showed no association on analysis including all individuals regardless of alcohol intake, but for which an association emerged on stratification by alcohol intake.



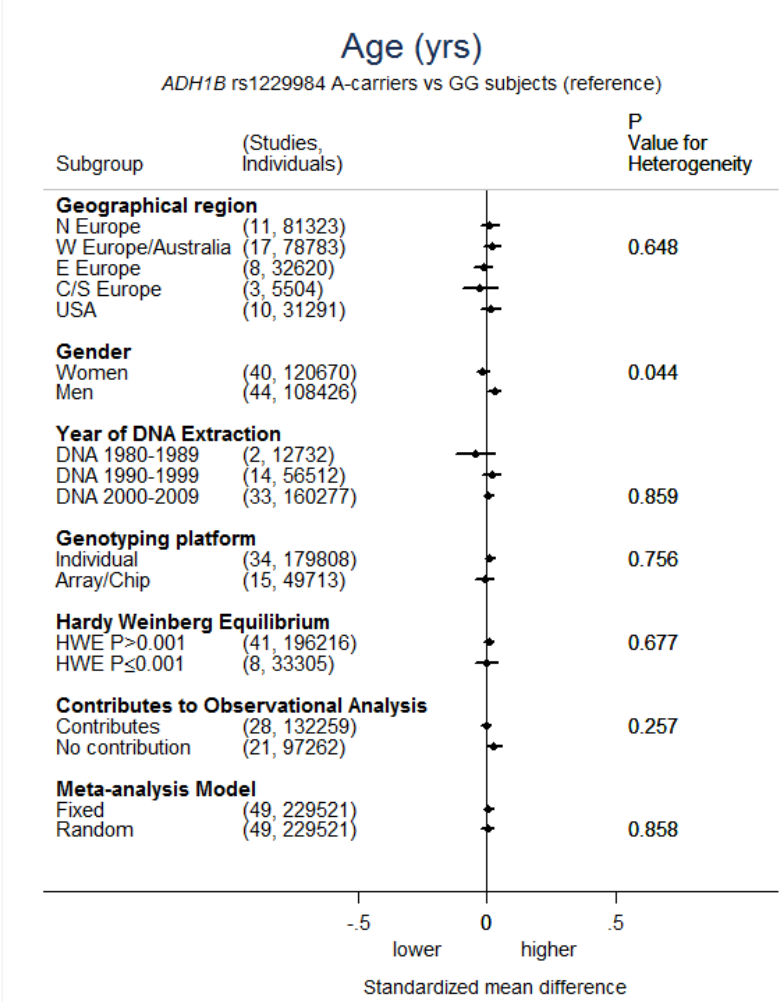
Footnotes: † for log(e) transformed traits, the percentage difference in the geometric mean is reported rather than the mean difference. Alcohol units are British; to convert from British to US units, divide by 1.75 (i.e. 1 British unit=10 ml or 7.9g ethanol = 0.57 US units). . P value for heterogeneity represents a test for trend derived from meta-regression (see **Supplementary Methods 2.3**). The "Light-Mod" stratum is short for "Light-to-Moderate."

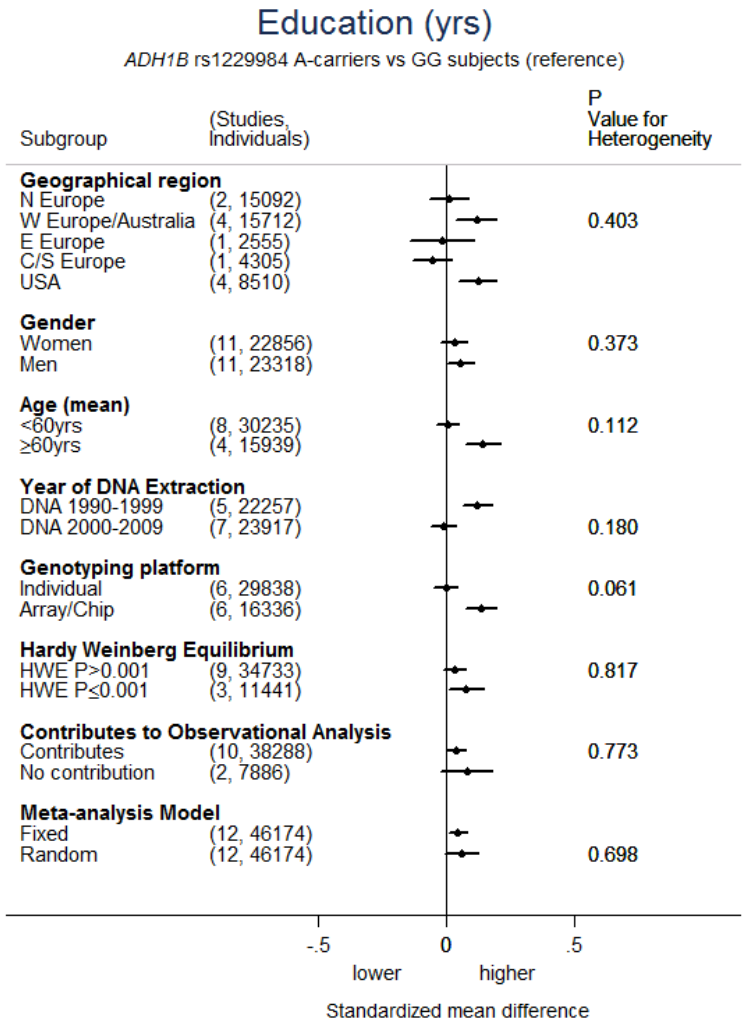
Figure S10. Meta-analysis pooled estimates of the association between *ADH1B* rs1229984 (A-allele carriers vs. GG-subjects) and lifestyle traits and liver enzyme overall and stratified by alcohol intake

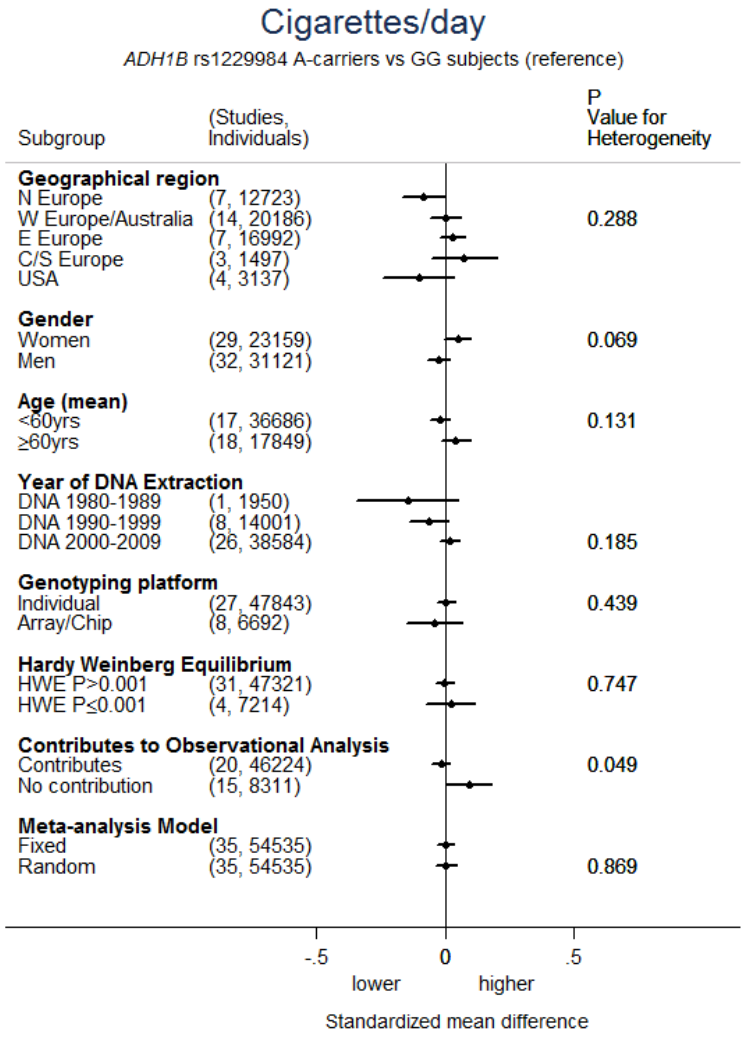


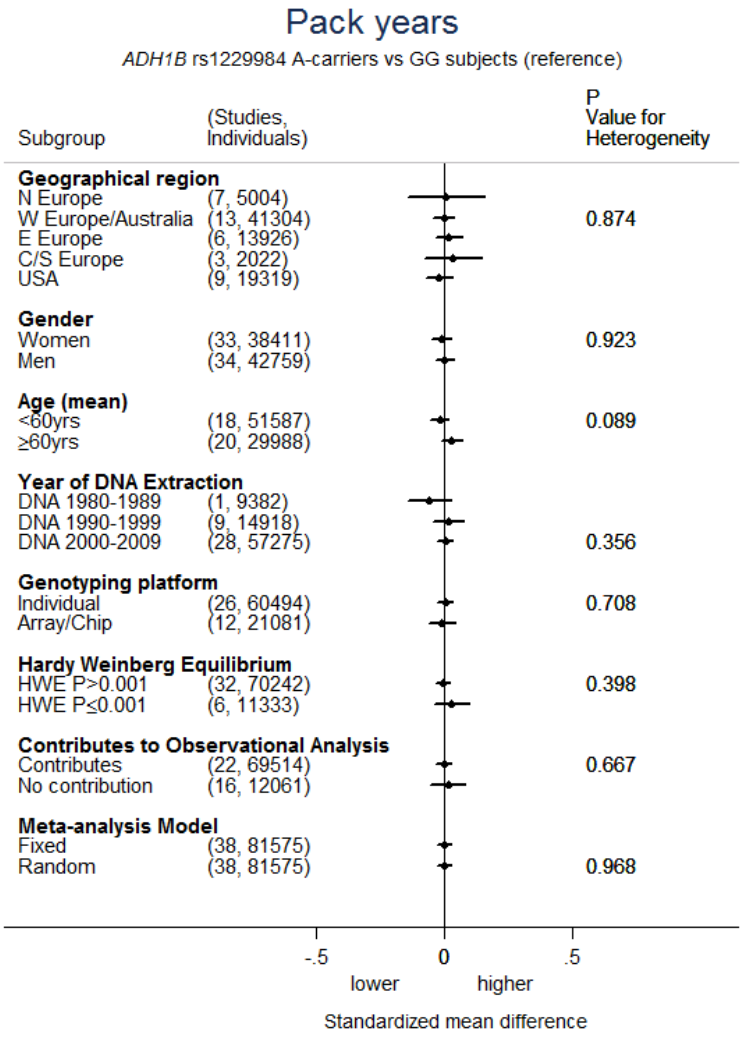
Footnote: The alcohol groups are: none (0 units/week); light-to-moderate (>0 to <21 units/week) and heavy (≥21 units/week). Alcohol units are British; to convert from British to US units, divide by 1.75 (i.e. 1 British unit=10 ml or 7.9g ethanol = 0.57 US units). P value for heterogeneity represents a test for trend (see **Supplementary Methods 2.3**). The "All individuals" estimates (colored red) also include studies without measures of alcohol.

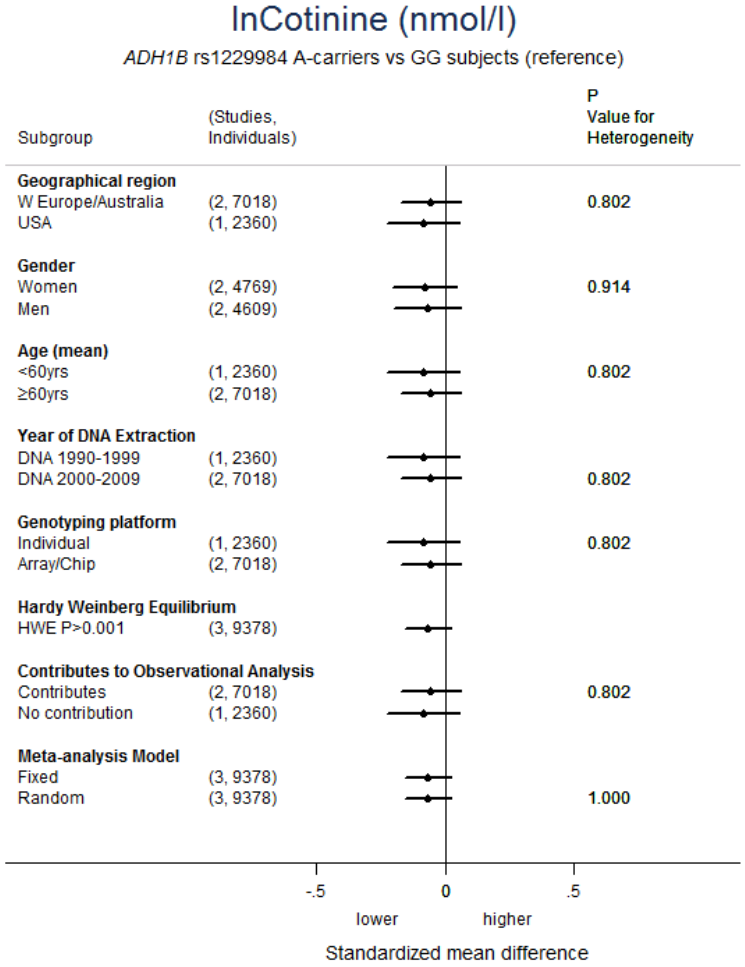
Figure S11. Subgroup analysis of the association between *ADH1B* rs1229984 (A-allele carriers vs. GG-subjects) and lifestyle factors

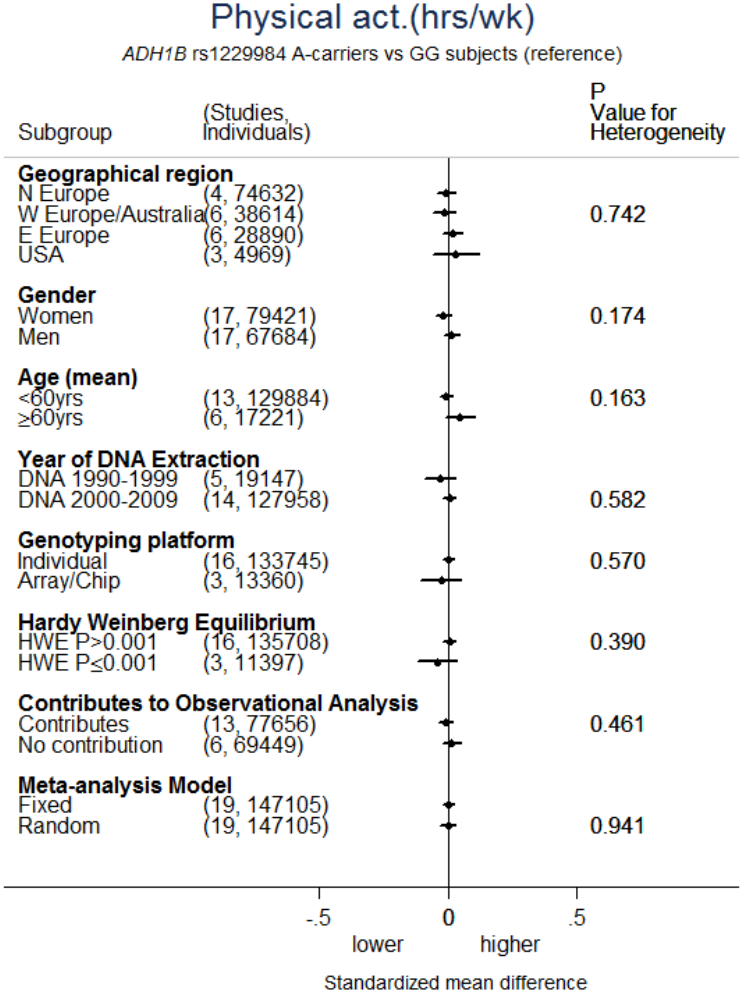





Cigarettes/day
ADH1B rs1229984 A-carriers vs GG subjects (reference)
Subgroup
(Studies, Individuals)
P Value for Heterogeneity
Geographical region
N Europe (7, 12723)
W Europe/Australia (14, 20186) 0.288
E Europe (7, 16992)
C/S Europe (3, 1497)
USA (4, 3137)
Gender
Women (29, 23159) 0.069
Men (32, 31121)
Age (mean)
<60yrs (17, 36686) 0.131
≥60yrs (18, 17849)
Year of DNA Extraction
DNA 1980-1989 (1, 1950)
DNA 1990-1999 (8, 14001)
DNA 2000-2009 (26, 38584) 0.185
Genotyping platform
Individual (27, 47843) 0.439
Array/Chip (8, 6692)
Hardy Weinberg Equilibrium
HWE P>0.001 (31, 47321) 0.747
HWE P≤0.001 (4, 7214)
Contributes to Observational Analysis
Contributes (20, 46224) 0.049
No contribution (15, 8311)
Meta-analysis Model
Fixed (35, 54535)
Random (35, 54535) 0.869
-.5
0
.5
lower
higher
Standardized mean difference


Pack years
ADH1B rs1229984 A-carriers vs GG subjects (reference)
Subgroup
(Studies, Individuals)
P Value for Heterogeneity
Geographical region
N Europe (7, 5004)
W Europe/Australia (13, 41304) 0.874
E Europe (6, 13926)
C/S Europe (3, 2022)
USA (9, 19319)
Gender
Women (33, 38411) 0.923
Men (34, 42759)
Age (mean)
<60yrs (18, 51587) 0.089
≥60yrs (20, 29988)
Year of DNA Extraction
DNA 1980-1989 (1, 9382)
DNA 1990-1999 (9, 14918)
DNA 2000-2009 (28, 57275) 0.356
Genotyping platform
Individual (26, 60494) 0.708
Array/Chip (12, 21081)
Hardy Weinberg Equilibrium
HWE P>0.001 (32, 70242) 0.398
HWE P≤0.001 (6, 11333)
Contributes to Observational Analysis
Contributes (22, 69514) 0.667
No contribution (16, 12061)
Meta-analysis Model
Fixed (38, 81575)
Random (38, 81575) 0.968
-.5
0
.5
lower
higher
Standardized mean difference


lnCotinine (nmol/l)
ADH1B rs1229984 A-carriers vs GG subjects (reference)
Subgroup
(Studies, Individuals)
P Value for Heterogeneity
Geographical region
W Europe/Australia (2, 7018) 0.802
USA (1, 2360)
Gender
Women (2, 4769) 0.914
Men (2, 4609)
Age (mean)
<60yrs (1, 2360) 0.802
≥60yrs (2, 7018)
Year of DNA Extraction
DNA 1990-1999 (1, 2360)
DNA 2000-2009 (2, 7018) 0.802
Genotyping platform
Individual (1, 2360) 0.802
Array/Chip (2, 7018)
Hardy Weinberg Equilibrium
HWE P>0.001 (3, 9378)
Contributes to Observational Analysis
Contributes (2, 7018) 0.802
No contribution (1, 2360)
Meta-analysis Model
Fixed (3, 9378)
Random (3, 9378) 1.000
-.5
0
.5
lower
higher
Standardized mean difference


Physical act.(hrs/wk)
ADH1B rs1229984 A-carriers vs GG subjects (reference)
Subgroup
(Studies, Individuals)
P Value for Heterogeneity
Geographical region
N Europe (4, 74632)
W Europe/Australia (6, 38614) 0.742
E Europe (6, 28890)
USA (3, 4969)
Gender
Women (17, 79421) 0.174
Men (17, 67684)
Age (mean)
<60yrs (13, 129884) 0.163
≥60yrs (6, 17221)
Year of DNA Extraction
DNA 1990-1999 (5, 19147)
DNA 2000-2009 (14, 127958) 0.582
Genotyping platform
Individual (16, 133745) 0.570
Array/Chip (3, 13360)
Hardy Weinberg Equilibrium
HWE P>0.001 (16, 135708) 0.390
HWE P≤0.001 (3, 11397)
Contributes to Observational Analysis
Contributes (13, 77656) 0.461
No contribution (6, 69449)
Meta-analysis Model
Fixed (19, 147105)
Random (19, 147105) 0.941
-.5
0
.5
lower
higher
Standardized mean difference

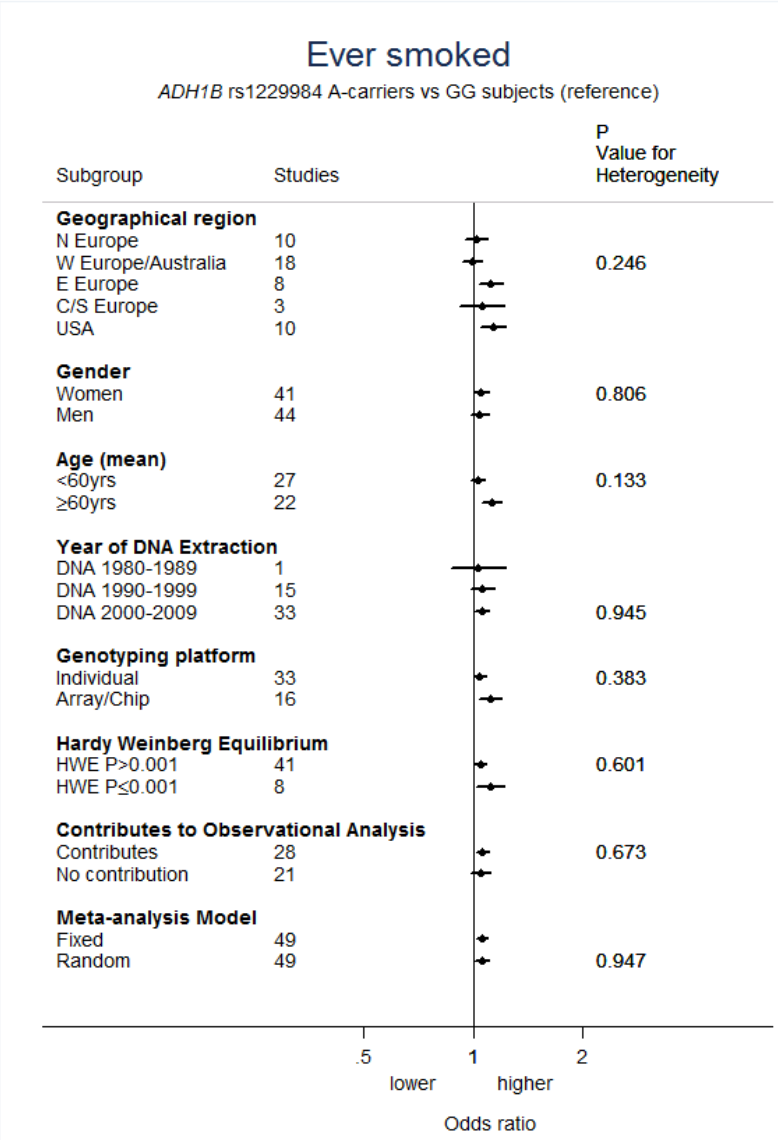
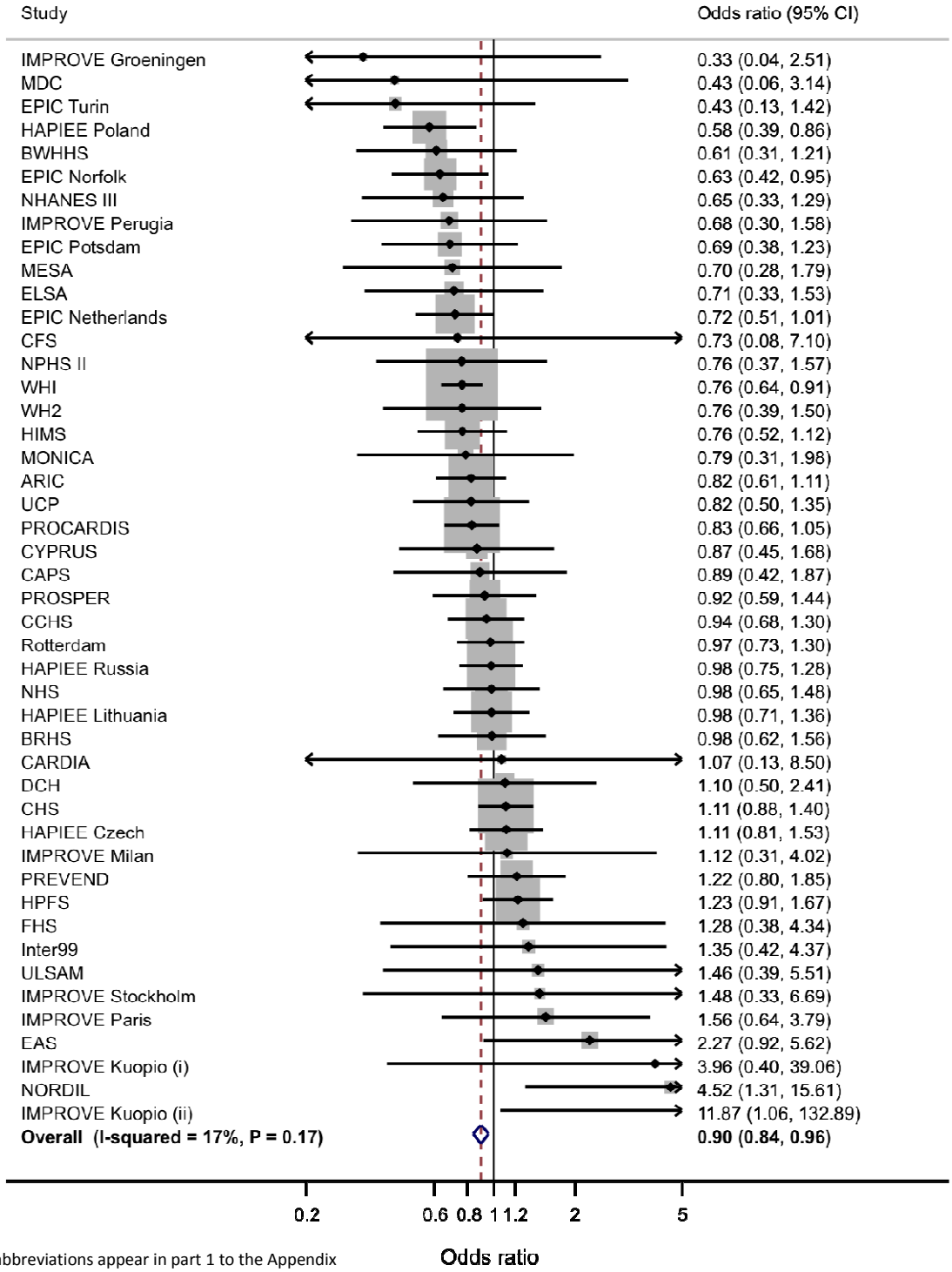

Ever smoked
ADH1B rs1229984 A-carriers vs GG subjects (reference)
Subgroup
Studies
P Value for Heterogeneity
Geographical region
N Europe 10
W Europe/Australia 18 0.246
E Europe 8
C/S Europe 3
USA 10
Gender
Women 41 0.806
Men 44
Age (mean)
<60yrs 27 0.133
≥60yrs 22
Year of DNA Extraction
DNA 1980-1989 1
DNA 1990-1999 15
DNA 2000-2009 33 0.945
Genotyping platform
Individual 33 0.383
Array/Chip 16
Hardy Weinberg Equilibrium
HWE P>0.001 41 0.601
HWE P≤0.001 8
Contributes to Observational Analysis
Contributes 28 0.673
No contribution 21
Meta-analysis Model
Fixed 49
Random 49 0.947
.5
1
2
lower
higher
Odds ratio

Figure S12. Meta-analysis of the association between *ADH1B* rs1229984 (A-allele carriers vs. GG-subjects) and coronary heart disease



Study abbreviations appear in part 1 to the Appendix (Studies included in the *ADH1B* collaboration)

Figure S13. Meta-analysis of the association between *ADH1B* rs1229984 (A-allele carriers vs. GG-subjects) and ischemic stroke

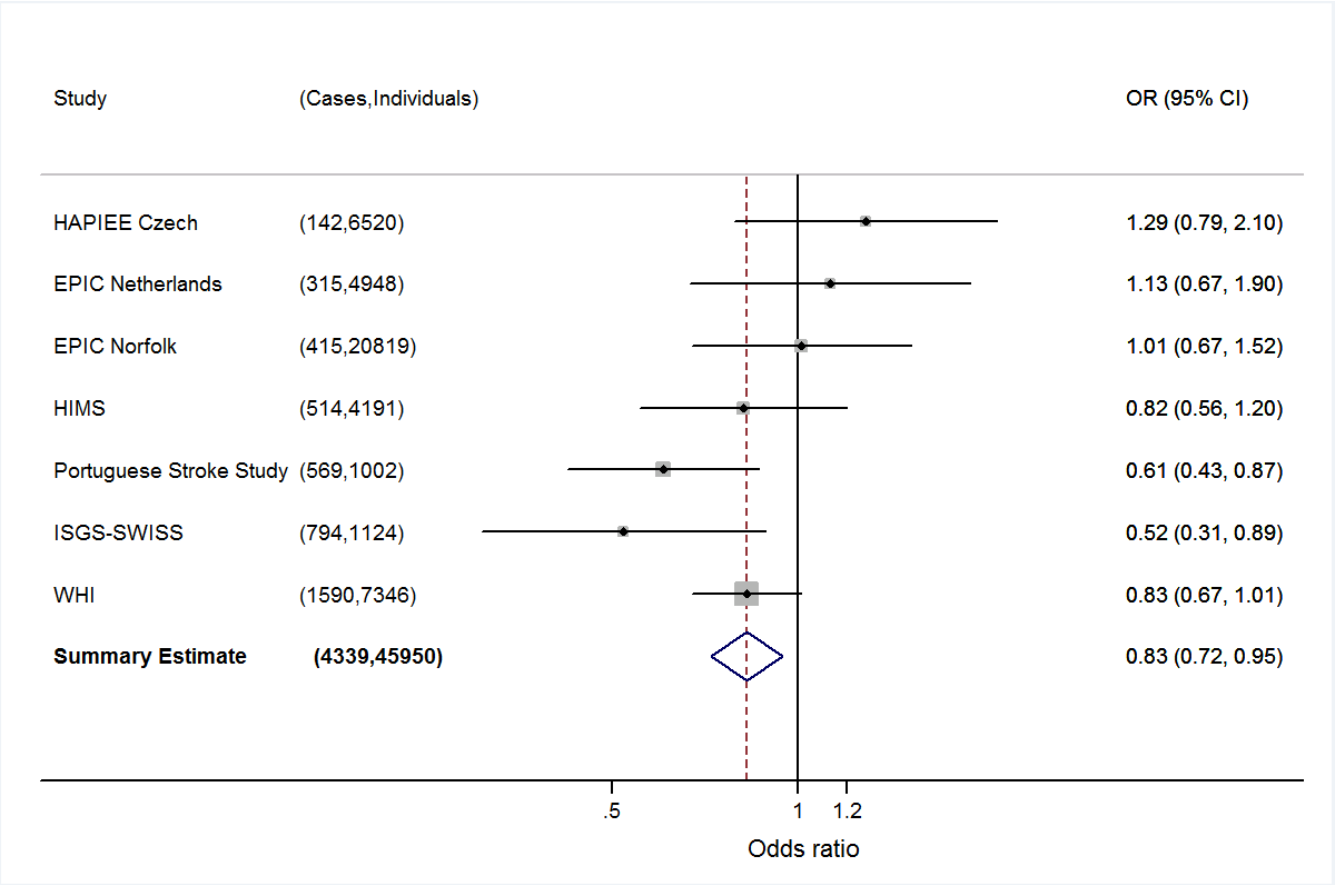
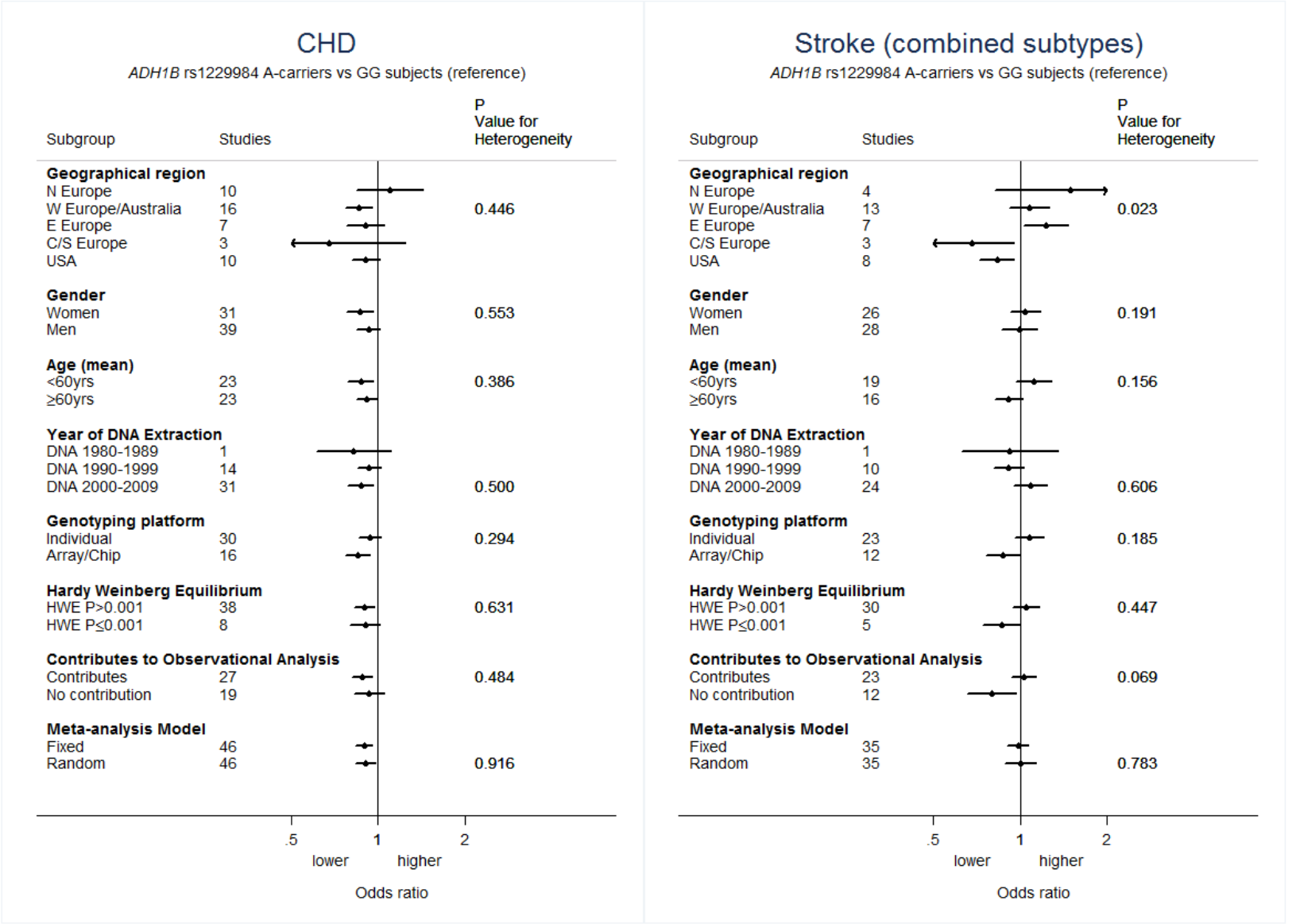
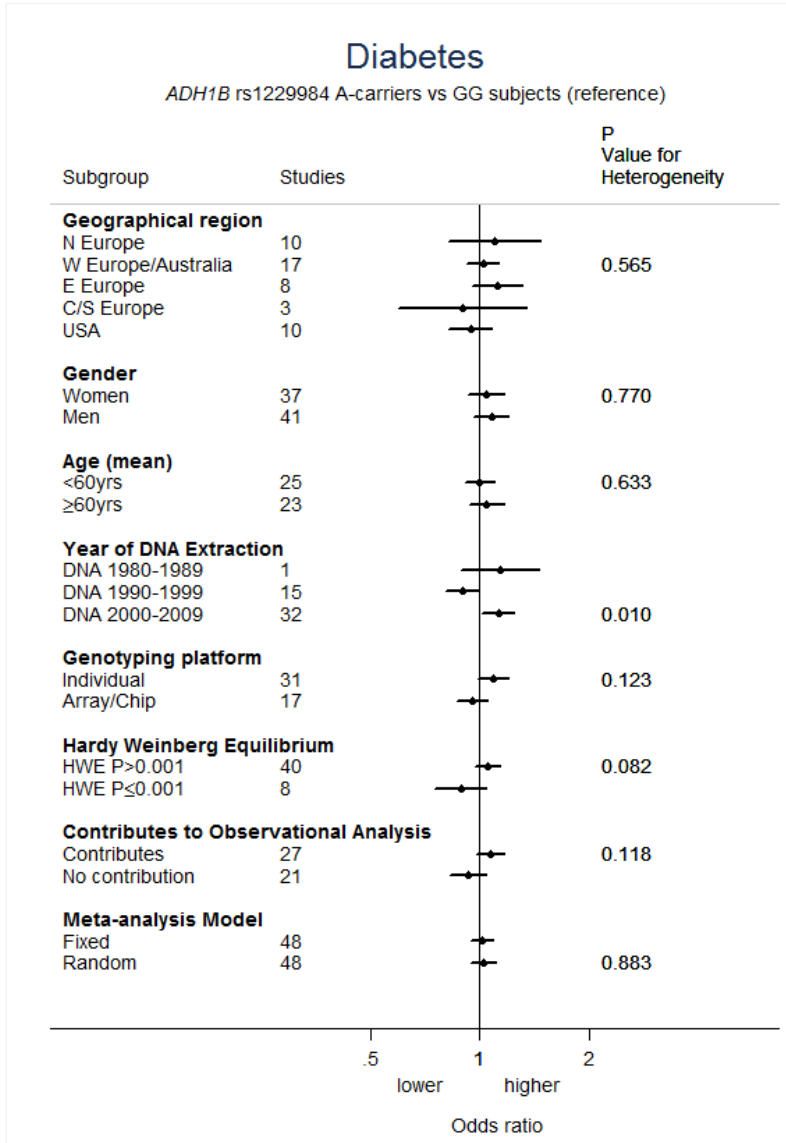


Figure S14. Subgroup analysis of the association between *ADH1B* rs1229984 (A-allele carriers vs. GG-subjects) and cardiometabolic disorders




Diabetes
ADH1B rs1229984 A-carriers vs GG subjects (reference)
Subgroup
Studies
P Value for Heterogeneity
Geographical region
N Europe 10
W Europe/Australia 17 0.565
E Europe 8
C/S Europe 3
USA 10
Gender
Women 37 0.770
Men 41
Age (mean)
<60yrs 25 0.633
≥60yrs 23
Year of DNA Extraction
DNA 1980-1989 1
DNA 1990-1999 15
DNA 2000-2009 32 0.010
Genotyping platform
Individual 31 0.123
Array/Chip 17
Hardy Weinberg Equilibrium
HWE P>0.001 40 0.082
HWE P≤0.001 8
Contributes to Observational Analysis
Contributes 27 0.118
No contribution 21
Meta-analysis Model
Fixed 48
Random 48 0.883
.5
1
2
lower
higher
Odds ratio

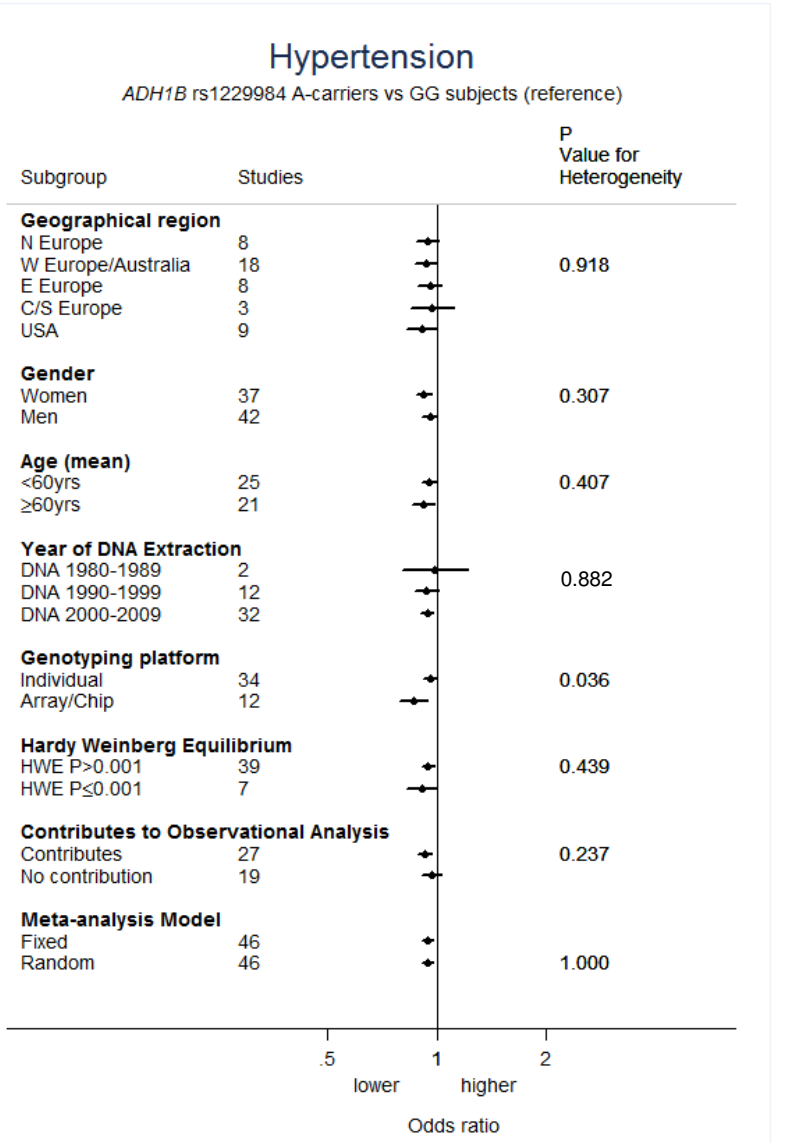
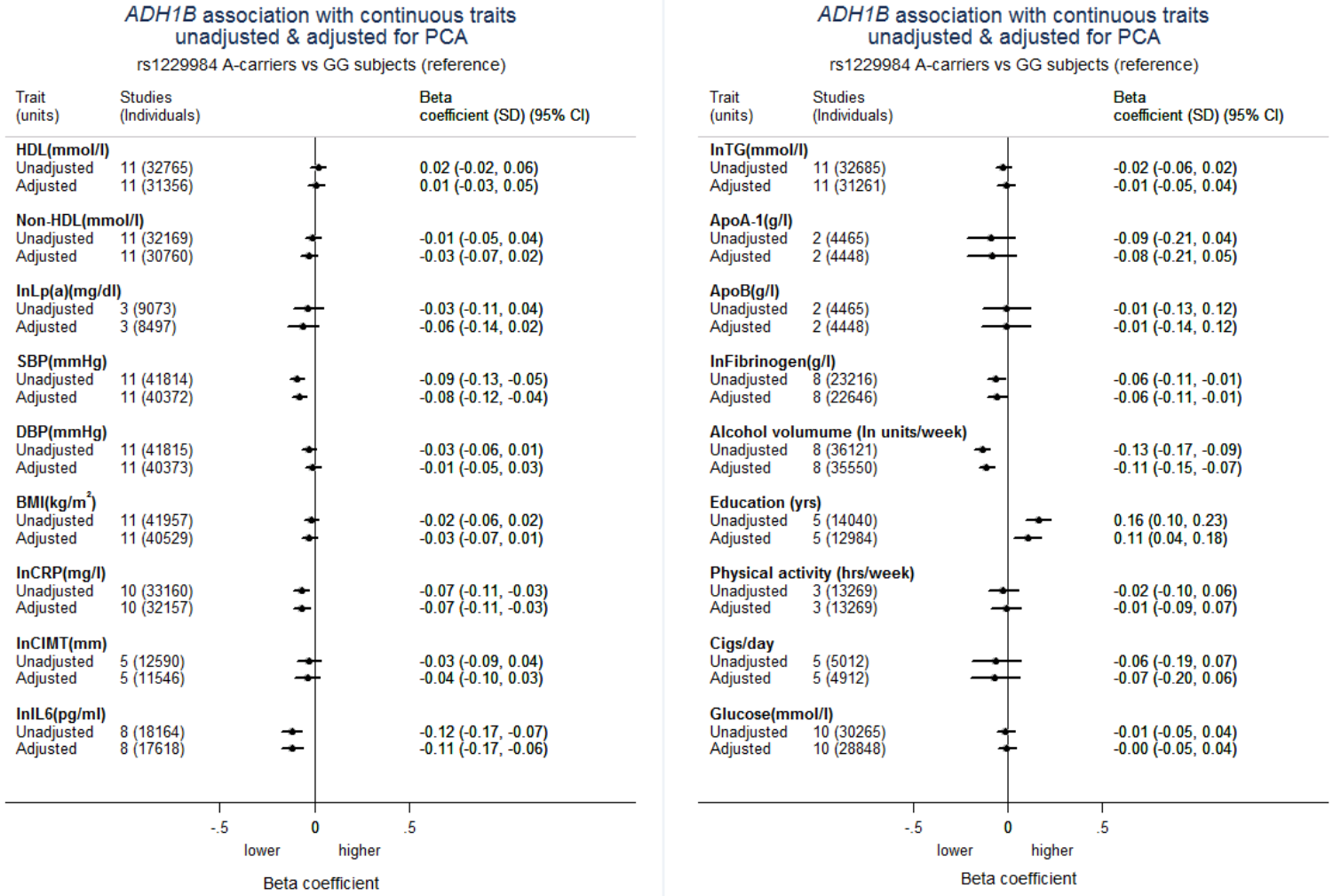
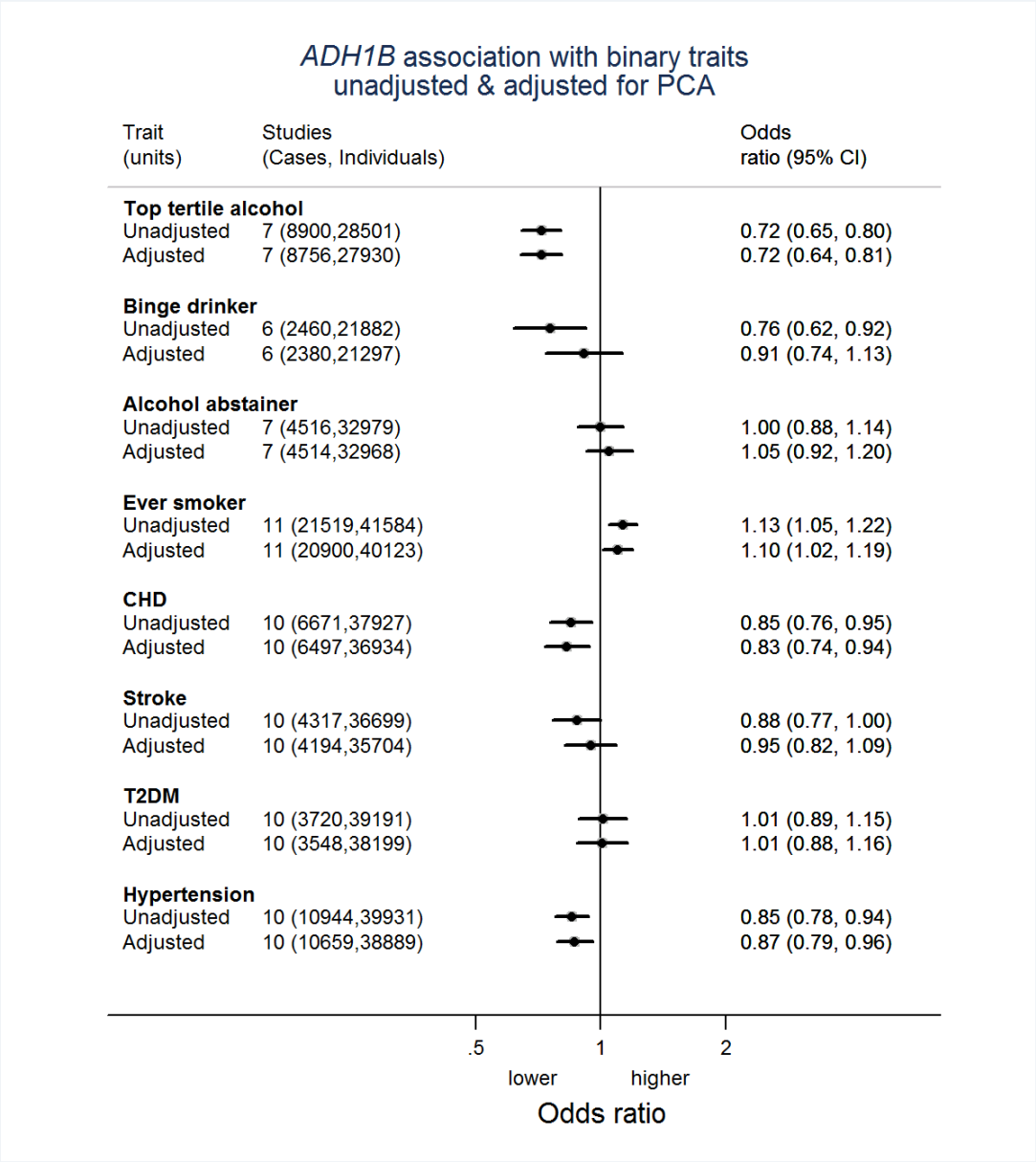

Hypertension
ADH1B rs1229984 A-carriers vs GG subjects (reference)
Subgroup
Studies
P Value for Heterogeneity
Geographical region
N Europe 8
W Europe/Australia 18 0.918
E Europe 8
C/S Europe 3
USA 9
Gender
Women 37 0.307
Men 42
Age (mean)
<60yrs 25 0.407
≥60yrs 21
Year of DNA Extraction
DNA 1980-1989 2 0.882
DNA 1990-1999 12
DNA 2000-2009 32
Genotyping platform
Individual 34 0.036
Array/Chip 12
Hardy Weinberg Equilibrium
HWE P>0.001 39 0.439
HWE P≤0.001 7
Contributes to Observational Analysis
Contributes 27 0.237
No contribution 19
Meta-analysis Model
Fixed 46
Random 46 1.000
.5
1
2
lower
higher
Odds ratio

Figure S15. Meta-analysis pooled estimates of the association between *ADH1B* rs1229984 (A-allele carriers vs. GG-subjects) and continuous traits adjusted for principal components analysis



Footnote: Beta coefficient (SD) represents the beta coefficient per standard deviation of each trait

Figure S16. Meta-analysis pooled estimates of the association between *ADH1B* rs1229984 (A-allele carriers vs. GG-subjects) and binary traits adjusted for principal components analysis



5. Supplementary Tables

Table S1. Design and genotyping characteristics of studies included in the collaboration

Study	Study design	Sampling Frame	N with DNA in this analysis	Year of blood sampling used for DNA extraction	Genotyping method	Country	Contributes to obser-vational analysis	Published prior to joining consortium	Hardy Weinberg Equilibrium P value	Call rate (%)
ALSPAC	Cohort	Pregnant women (Avon County)	2557	1991-2010	KASPar	UK	N	N	0.410	97.7
ARIC	Cohort	Community	9557	1987-89	IBC 50k CardioChip	USA	Y	N	0.705	97.8
BRHS	Cohort	General practices	3843	1998-2000	KASPar	UK	Y	N	0.42	100
BWHHS	Cohort	General practices	3412	1999-2001	IBC 50k CardioChip	UK	Y	N	0.912	99.7
CaPS	Cohort	Electoral register & General practices	1102	1993-1994	KASPar	UK	Y	N	0.460	98.4
CARDIA	Cohort	Community	1433	1995-1996	IBC 50k CardioChip	USA	Y	N	4.97E-04	97.3
CCHS	Cohort	Population	9081	1991-94	Nanogen	Denmark	Y	Y	0.522	99.6
CFS	Cohort	Family	134	2001-2006	IBC 50k CardioChip	USA	N	N	0.462	98.0
CGPS	Cohort	Population	57041	2003-ongoing	TaqMan	Denmark	N	Y	0.473	98.0
CHS	Cohort	Community	3936	1992–1993	IBC 50k CardioChip	USA	Y	N	0.001	97.9
CYPRUS	Cohort	Community	730	2003-2008	TaqMan	Cyprus	Y	N	0.081	99.9
Czech post-MONICA	Cohort	Administrative districts	2558	2000-2001	PCR-RFLP	Czech Republic	Y	N	0.801	97.9

Study	Study design	Sampling Frame	N with DNA in this analysis	Year of blood sampling used for DNA extraction	Genotyping method	Country	Contributes to obser-vational analysis	Published prior to joining consortium	Hardy Weinberg Equilibrium P value	Call rate (%)
DCH	Nested case cohort	General population (born in Denmark)	2736	1993-97	TaqMan	Denmark	Y	Y	0.203	91.8
EAS	Cohort	General practices	873	2004	TaqMan	UK	Y	N	0.693	95.6
ELSA	Cohort	Respondents of HSE	5450	2004	KASPar	UK	Y	N	0.263	98.8
EPIC InterAct	Nested case cohort	Population	9427	1991-1998	Metabochip plus	Denmark, France, Germany, Italy, Netherlands, Spain, Sweden, UK	N	N	0.0013	99.6
EPIC Netherlands	Nested case control	Population (Bilthoven & Utrecht)	5186	1993 and 1997	IBC 50k CardioChip	The Netherlands	N	N	0.095	99.9
EPIC Norfolk	Nested case control	Population (Norwich & E Anglia)	20195	1997-2000	TaqMan	UK	Y	N	0.091	99
EPIC Potsdam	Nested case cohort	Population (Potsdam (Germany)	2253	2007	TaqMan	Germany	N	Y	0.454	98.8
EPIC Turin	Cohort	Population (Torino area)	4526	2008	TaqMan	Italy	Y	N	0.362	99
FHS	Cohort	Community	1082	1948-present	IBC 50k CardioChip	USA	Y	N	0.002	99
HAPIEE Czech	Cohort	City districts	6678	2003-2005	KASPar	Czech Republic	Y	N	0.745	98.6
HAPIEE Lithuania	Cohort	City districts	6936	2006-2008	KASPar	Lithuania	Y	N	0.149	98.6
HAPIEE Poland	Cohort	City districts	5729	2003-2005	KASPar	Poland	Y	N	0.238	97.0
HAPIEE Russia	Cohort	City districts (Novosibirsk City)	7083	2003-2005	KASPar	Russia	Y	N	0.041	98.8

Study	Study design	Sampling Frame	N with DNA in this analysis	Year of blood sampling used for DNA extraction	Genotyping method	Country	Contributes to obser-vational analysis	Published prior to joining consortium	Hardy Weinberg Equilibrium P value	Call rate (%)
HIMS	Cohort	City population	4191	2001-04	TaqMan	Australia	Y	N	4.06E-08	98.7
HPFS	Nested case control	Health Professionals	1264	1994	TaqMan	USA	N	N	0.45	93
IMPROVE Groningen	Cohort	Clinic	421	2004-2005	TaqMan	Netherlands	N	N	0.109	>99
IMPROVE Kuopio 1	Cohort	Clinic	481	2004-2005	TaqMan	Finland	N	N	0.927	>99
IMPROVE Kuopio 2	Cohort	Clinic	440	2004-2005	TaqMan	Finland	N	N	0.943	>99
IMPROVE Milan	Cohort	Clinic	514	2004-2005	TaqMan	Italy	N	N	0.574	>99
IMPROVE Paris	Cohort	Clinic	436	2004-2005	TaqMan	France	N	N	0.008	>99
IMPROVE Perugia	Cohort	Clinic	464	2004-2005	TaqMan	Italy	N	N	0.347	>99
IMPROVE Stockholm	Cohort	Clinic	480	2004-2005	TaqMan	Sweden	N	N	3.43E-09	>99
Inter99	RCT	Population	6332	1999-2001	KASPar	Denmark	Y	Y	6.16E-27	97.6
ISGS-SWISS	Case control	Clinic	1124	2002-2008	TaqMan	USA	N	N	1.000	>99
Izhevsk	Case control	Population-based controls from CC	653	2008-2009	PCR + electrophoresis	Russia	Y	N	0.192	>99
MDC	Cohort	Population	1937	1991-1996	IBC 50k CardioChip	Sweden	N	N	0.537	>99
MESA	Cohort	Population	2293	2000-2002	IBC 50k CardioChip	USA	Y	N	0.012	97
MRC 1958BC	Cohort	Population	2587	2002-2004	Illumina 1.2M	UK	N	N	0.2609	95.4
MRC NSHD	Cohort	Population (born March 1946)	2696	1999	KASPar	UK	N	N	0.222	>99

Study	Study design	Sampling Frame	N with DNA in this analysis	Year of blood sampling used for DNA extraction	Genotyping method	Country	Contributes to obser-vational analysis	Published prior to joining consortium	Hardy Weinberg Equilibrium P value	Call rate (%)
NHANES III	Cross-sectional	General population	2388	1991-1994	TaqMan	USA	N	N	1.000	98
NHS	Nested case control	Nurses	1322	1990	TaqMan	USA	N	N	<2.2E-16	97
NORDIL	RCT	Clinic	1921	1992-1999	IBC 50k CardioChip	Norway and Sweden	N	N	1.000	>99
NPHS II	Cohort	General practices	2659	2000	TaqMan	UK	Y	N	0.874	96.1
Portuguese Stroke Study	Case control	Clinic	1002	1995 and 1998	TaqMan	Portugal	N	N	0.006	99.4
PREVEND	Cohort	Mixed population (Groningen City)	7729	1997-1998	KASPar	Netherlands	N	N	3.05E-09	>95
PROCARDIS	Case control	Hospital	6440	1999-2005	IBC 50k CardioChip	Germany, Italy, Sweden, UK	N	N	1.000	>99
PROSPER	RCT	Elderly; cholesterol 4-9 mmol/l	5504	1997-1999	TaqMan	Scotland, Ireland, The Netherlands	N	N	0.008	95.5
Rotterdam	Cohort	Administrative district	5827	1992	TaqMan	Netherlands	Y	N	0.341	>90
SMART	Cohort	Atherosclerosis hospital referrals	7917	1996-2006	KASPAR	Netherlands	N	N	3.85E-24	97.0
TPT	RCT	Acute coronary syndrome	3175	1984-1989	TaqMan	UK	N	N	0.680	86.2
UCP	Nested case control	Hospital patients	1615	2007	IBC 50k CardioChip	Netherlands	N	N	1.000	100
ULSAM	Cohort	General population (Uppsala County)	453	2004	Illumina Golden Gate	Sweden	Y	N	0.775	98.9
Whitehall II	Cohort	Workplace (civil servants)	5029	2002-2004	IBC 50k CardioChip	UK	Y	N	0.106	99.3

Study	Study design	Sampling Frame	N with DNA in this analysis	Year of blood sampling used for DNA extraction	Genotyping method	Country	Contributes to obser-vational analysis	Published prior to joining consortium	Hardy Weinberg Equilibrium P value	Call rate (%)
WHI	Nested case control	Community	7882	1993-1998	IBC 50k CardioChip	USA	Y	N	3.15E-25	99.2

Table S2. Characteristics of the alcohol questionnaires used in the collaborating studies

Study	Questionnaire beverage specific	Binge drinker	Alcohol Abstainer
ALSPAC	NA	NA	NA
ARIC	Y	>70g/ day	Self-declared abstainer at first wave
BRHS	Y	> 6 drinks / occasion	Never consumed alcoholic drinks
BWHHS	Y	> 6 drinks/ day	Never drank at baseline
CaPS	Y	≥ 5 drinks/ normal occasion	Not drinking at 5 waves
CARDIA	Y	> 5 drinks on day drank most in past month	Not drinking at 4 waves
CCHS	Y	NA	NA
CFS	NA	NA	Never drink alcohol
CGPS	Y	>14 units for women or >21 units for men per week and not drinking daily	NA
CHS	Y	≥5 drinks per day	NA
Cyprus	Y	NA	NA
Czech post-MONICA	Y	NA	No drinking in past six months
DCH	Y	NA	Answering never drink to all beverages
EAS	Y	> 5 drinks on day drank most	NA
ELSA	Y	> 10 units on heaviest day in last 7	Always an abstainer
EPIC-InterAct	Y	NA	NA
EPIC Netherlands	Y	NA	Never drink alcohol
EPIC Norfolk	Y	NA	Never drank alcohol in the past
EPIC-Potsdam	Y	NA	Never drank alcohol in the past
EPIC Turin	Y	NA	Never drank beer/ wine/ spirits

Study	Questionnaire beverage specific	Binge drinker	Alcohol Abstainer
FHS	Y	≥5 beverage specific drinks at one time	NA
HAPIEE Czech	N	≥5 drinks/ day	Answering never drink to all beverages
HAPIEE Lithuania	N	≥5 drinks/ day	Answering never drink to all beverages
HAPIEE Poland	N	≥5 drinks/ day	Answering never drink to all beverages
HAPIEE Russia	N	≥5 drinks/ day	Answering never drink to all beverages
HIMS	N	≥5+ drinks on usual drinking day	Never drank alcohol
HPFS	N	>6 drinks on largest day in typical month	Self-declared abstainer (in 1994)
IMPROVE	Y	NA	NA
Inter99	Y	≥5 drinks at least once/ week	Self-declared abstainer in past year
ISGS-SWISS	N	NA	Self-declared abstainer/rare drinker in past year
Izhevsk	Y	≥5 drinks on one occasion	Never drank in life other than few occasions
MDC	Y	NA	NA
MESA	Y	> 5 drinks on day drank most	Not drinking at 4 waves
MRC 1958BC	NA	NA	NA
MRC NHSD	Y	NA	NA
NHANES III	N	≥ 5 drinks on any day in the past 12 months	Less than 12 drinks in entire life
NHS	N	NA	Self-declared abstainer (in 1990)
NORDIL	NA	NA	NA
NPHS II	Y	NA	NA
Portuguese Stroke Study	NA	NA	NA
PREVEND	N	NA	Almost never drank

Study	Questionnaire beverage specific	Binge drinker	Alcohol Abstainer
PROCARDIS	NA	NA	NA
PROSPER	N	NA	NA
Rotterdam	Y	>6 alcoholic beverages on one day during the last year	Self-declared abstainer in past year
SMART	NA	NA	NA
TPT	NA	NA	NA
UCP	Y	NA	Self-declared “never used alcohol”
ULSAM	Y	NA	Self-declared abstainer(age 60)
WHITEHALL II	N	> 5 beers or wine / spirits in one sitting	Non-drinker at 3 waves
WHI	Y	NA	Less than 12 drinks in entire life

Footnote: NA: not available

Table S3. Event definitions in studies included in the collaboration

	Coronary heart disease					Stroke (combined subtypes)					Diabetes		
	Non-fatal			Fatal		Non-fatal			Fatal		Non-fatal		
Study	Self report	Medical records	Clinical/lab. measures	Death certificate	ICD coded	Self report	Medical records	Clinical/lab. /imaging measures	Death certificate	ICD coded	Self report	Medical records	Clinical/lab. measures
ALSPAC													
ARIC		•		•	•		•		•	•		•	•
BRHS		•		•	•		•		•	•		•	
BWHHS	•	•		•	•	•	•		•	•	•	•	
CaPS	•	•		•	•	•	•		•	•	•	•	•
CARDIA		•		•			•		•			•	
CCHS		•		•	•		•		•	•	•		
CFS	•					•						•	
CGPS													
CHS	•	•		•	•	•	•		•	•	•		•
Cyprus	•	•	•			•	•				•		•
Czech post-MONICA	•			•		•			•		•		•
DCH		•		•	•		•		•	•	•		
EAS	•	•	•	•	•	•	•		•	•	•		
ELSA	•				•	•	•			•	•		•
EPIC InterAct											•	•	
EPIC Norfolk		•		•	•		•		•	•	•	•	
EPIC Netherlands		•		•	•		•		•	•	•	•	
EPIC Potsdam		•		•	•	•						•	
EPIC Turin		•	•	•	•		•	•	•	•		•	•
FHS		•		•			•		•			•	
HAPIEE Czech	•	•	•	•	•	•	•	•	•	•	•		
HAPIEE Lithuania	•	•	•	•	•	•	•	•	•	•	•		
HAPIEE Poland	•	•	•	•	•	•	•	•	•	•	•		
HAPIEE Russia	•	•	•	•	•	•	•	•	•	•	•		
HIMS	•	•		•	•	•	•		•	•	•	•	•

	Coronary heart disease					Stroke (combined subtypes)					Diabetes		
	Non-fatal			Fatal		Non-fatal			Fatal		Non-fatal		
Study	Self report	Medical records	Clinical/lab. measures	Death certificate	ICD coded	Self report	Medical records	Clinical/lab. /imaging measures	Death certificate	ICD coded	Self report	Medical records	Clinical/lab. measures
HPFS	●	●		●	●	●					●		
IMPROVE	●	●		●		●	●		●		●	●	●
Inter99	●					●					●		●
ISGS-SWISS							●	●	●				
Izhevsk											●		
MDC		●	●	●	●		●	●	●	●	●	●	●
MESA	●					●					●		
MRC 1958BC											●		●
MRC NSHD	●					●					●		
NHANES III	●					●					●		
NHS	●	●		●	●	●					●		
NORDIL		●	●	●	●		●	●	●	●	●	●	●
NPHS-II	●	●		●	●	●	●		●	●	●	●	
Portuguese Stroke Study							●	●					
PREVEND		●		●	●		●		●	●		●	
PROCARDIS		●	●										
PROSPER		●	●	●	●		●	●	●	●		●	●
Rotterdam		●	●				●	●				●	●
SMART													
TPT		●		●			●		●			●	
UCP		●											
ULSAM		●		●	●		●		●	●	●	●	●
Whitehall II		●		●			●		●			●	●
WHI	●					●					●		

Table S4. General and alcohol characteristics of studies included in the collaboration

Study Name	Age (yrs)		Gender (male)	Median Alcohol (British units/week)		Ln units/week (alcohol in British units) †		Binge drinking (≥5 drinks in one setting)	Self-declared non-drinker	Ln GGT (IU/L)	
	N	mean (SD)	Proportion (%)	Men	Women	N	mean (SD)	Proportion (%)	Proportion (%)	N	mean (SD)
ALSPAC	2557	47.75(4.31)	0.00	NA	NA	NA	NA	NA	NA	NA	NA
ARIC	9557	54.28(5.69)	46.46	2	0	9532	0.98(1.26)	0.62	18.15	NA	NA
BRHS	3843	68.74(5.51)	100.00	8	NA	3789	1.94(1.28)	7.32	3.35	3790	3.35(0.60)
BWHHS	3412	68.86(5.51)	0.00	NA	0	3407	0.99(1.19)	0.28	16.24	3334	3.12(0.63)
CaPS	1102	51.71(4.37)	100.00	14	NA	1061	2.4(1.23)	40.20	2.12	NA	NA
CARDIA	1433	25.58(3.37)	46.34	11	5	1433	1.89(1.22)	38.03	4.40	1427	1.86(0.60)
CCHS	9081	58.38(15.09)	44.49	15	5	8985	2.03(1.31)	NA	NA	8254	3.59(0.64)
CFS	134	53.20(14.75)	57.46	NA	NA	NA	NA	NA	46.97	NA	NA
CGPS	57041	56.10(13.30)	43.63	18	9	56970	2.37(1.10)	15.96	9.73	56997	3.45(0.57)
CHS	3936	72.78(5.60)	43.83	1	0	3919	0.83(1.18)	9.16	NA	NA	NA
Cyprus	730	60.48(10.21)	46.85	2	0	729	0.64(0.92)	NA	NA	NA	NA
Czech post-MONICA	2558	48.76(10.73)	46.44	11	0	2558	1.38(1.34)	NA	38.58	NA	NA
DCH	2736	56.71(4.47)	62.02	17	7	2735	2.47(1.11)	NA	2.96	NA	NA
EAS	873	64.34(5.62)	49.37	7	1	873	1.44(1.19)	2.87	NA	872	3.21(0.61)
ELSA	5450	67.51(9.80)	45.56	10	3	5450	1.76(1.24)	6.39	3.66	NA	NA
EPIC InterAct	9427	54.00(9.70)	38.00	10	2	6090	1.66(1.26)	NA	NA	NA	NA
EPIC Netherlands	5186	54.06(10.11)	21.89	10	18	4381	2.20 (1.22)	NA	13.03	4339	3.23(0.52)
EPIC Norfolk	20195	59.29(9.23)	47.15	7	3	20005	1.59(1.03)	NA	14.22	NA	NA
EPIC-Potsdam	2253	50.64(9.01)	40.26	7	4	2253	2.05(1.11)	NA	0.53	2253	2.93(0.84)
EPIC Turin	4526	49.09(7.62)	62.62	24	3	4314	2.29(1.39)	NA	9.43	NA	NA
FHS	1082	45.70(10.10)	49.35	5	0	312	1.25(1.33)	5.05	NA	725	4.87(0.62)
HAPIEE Czech	6678	58.32(7.13)	45.91	15	1	6553	1.77(1.44)	22.15	11.68	900	3.24(0.62)
HAPIEE Lithuania	6936	60.96(7.58)	45.73	5	1	6899	1.14(1.15)	25.63	6.68	NA	NA
HAPIEE Poland	5729	57.61(6.94)	48.86	3	0	5654	1.04(1.49)	10.21	31.44	567	3.21(0.57)
HAPIEE Russia	7083	58.85(7.09)	43.10	3	0	7082	0.69(1.18)	25.87	16.29	7080	3.30(0.54)

Study Name	Age (yrs)		Gender (male)	Median Alcohol (British units/week)		Ln units/week (alcohol in British units) †		Binge drinking (≥5 drinks in one setting)	Self-declared non-drinker	Ln GGT (IU/L)	
	N	mean (SD)	Proportion (%)	Men	Women	N	mean (SD)	Proportion (%)	Proportion (%)	N	mean (SD)
HIMS	4191	71.11(4.22)	100.00	6	NA	4191	1.67(1.36)	6.16	5.81	NA	NA
HPFS	1264	64.35(8.57)	100.00	5	NA	1263	1.73(1.3)	6.01	14.64	NA	NA
IMPROVE Groeningen	421	63.85(6.05)	49.64	7	0	421	1.31(1.58)	NA	NA	NA	NA
IMPROVE Kuopio 1	481	63.93(5.44)	60.91	6	0	481	1.28(1.36)	NA	NA	NA	NA
IMPROVE Kuopio 2	440	64.43(5.52)	53.86	7	0	440	1.31(1.34)	NA	NA	NA	NA
IMPROVE Milan	514	65.28(5.75)	48.44	18	0	514	2(1.72)	NA	NA	NA	NA
IMPROVE Paris	436	64.34(6.34)	50.23	14	0	436	1.58(1.70)	NA	NA	NA	NA
IMPROVE Perugia	464	60.63(4.15)	24.14	27	0	464	1.67(1.60)	NA	NA	NA	NA
IMPROVE Stockholm	480	66.79(0.38)	51.46	11	5	480	1.71(1.42)	NA	NA	NA	NA
Inter99	6332	46.02(7.91)	48.89	15	4	6025	2.25(1.14)	36.65	9.83	NA	NA
ISGS-SWISS	780	72.06(14.99)	28.90	NA	NA	NA	NA	NA	59.57	NA	NA
Izhevsk	653	48.21(8.20)	100.00	10	NA	642	2.21(1.27)	55.44	0.46	653	3.5(0.76)
MDC	1937	57.78 (5.84)	57.61	10	5	1466	1.80(1.13)	NA	NA	NA	NA
MESA	2293	62.70(10.24)	52.25	7	2	2054	1.63(1.29)	12.09	22.99	NA	NA
MRC 1958BC	2585	NA	51.87	NA	NA	NA	NA	NA	NA	NA	NA
MRC NSHD	2696	53.00 (NA)	49.89	8	3	2696	1.64(1.15)	NA	NA	NA	NA
NHANES III	2388	53.10(20.6)	40	1	0	NA	NA	50.00	19.98	NA	NA
NHS	1322	59.95(6.45)	0.00	NA	1	1322	1.08(1.11)	3.33	37.90	NA	NA
NORDIL	1921	56.00(3.98)	51.17	NA	NA	NA	NA	NA	NA	NA	NA
NPHS II	2659	56.10(3.42)	100	6	NA	2659	1.85(1.23)	NA	NA	NA	NA
Portuguese Stroke Study	1002	62.90 (6.80)	0.00	NA	NA	NA	NA	NA	NA	NA	NA
PREVEND	7729	49.56(12.74)	49.24	5	1	7729	1.49(1.19)	NA	24.53	NA	NA
PROCARDIS	6440	60.72(9.04)	58.94	NA	NA	NA	NA	NA	NA	NA	NA
PROSPER	5504	75.33(3.36)	48.27	4	0	5504	1.08(1.16)	NA	NA	NA	NA
Rotterdam	5827	69.12(8.93)	41.07	9	1	4688	1.52(1.30)	6.59	20.44	4187	3.22(0.52)
SMART	8068	56.51 (12.40)	57.61	NA	NA	NA	NA	NA	NA	NA	NA

Study Name	Age (yrs)		Gender (male)	Median Alcohol (British units/week)		Ln units/week (alcohol in British units) †		Binge drinking (≥5 drinks in one setting)	Self-declared non-drinker	Ln GGT (IU/L)	
	N	mean (SD)	Proportion (%)	Men	Women	N	mean (SD)	Proportion (%)	Proportion (%)	N	mean (SD)
TPT	3175	57.3(6.76)	100.00	NA	NA	NA	NA	NA	NA	NA	NA
UCP	1615	62.78(9.65)	74.37	10	0	1323	1.75(1.33)	NA	12.30	NA	NA
ULSAM	453	71.29(0.44)	100.00	4	NA	421	1.58(1.06)	NA	15.65	NA	NA
Whitehall II	5029	43.87(5.94)	73.53	9	4	4990	2.01(1.08)	37.99	2.57	NA	NA
WHI	7882	67.98(6.58)	0.00	NA	0.5	7620	0.97(1.14)	NA	11.33	NA	NA

Footnote: † to preserve 0 values, a value of 1 was added to weekly units of alcohol prior to log transformation. NA: not available

Table S5. Number and proportion of outcomes in studies included in the collaboration

Study	Coronary heart disease		Stroke (combined sub-types)		Diabetes		Hypertension	
	N	Proportion (%)	N	Proportion (%)	N	Proportion (%)	N	Proportion (%)
ALSPAC	NA	NA	NA	NA	NA	NA	145	5.81
ARIC	985	10.37	510	5.37	1182	12.37	1195	12.51
BRHS	532	13.8	307	8.0	59	1.54	2551	66.38
BWHHS	303	13.7	290	8.00	338	9.91	2104	61.66
CaPS	193	28.47	NA	NA	10	0.91	685	62.16
CARDIA	10	0.70	4	0.28	99	6.91	26	1.81
CCCHS	993	10.94	NA	NA	303	3.34	4786	52.76
CFS	10	20.83	12	9.09	17	42.50	37	27.61
CGPS	NA	NA	NA	NA	NA	NA	30456	53.48
CHS	1694	43.03	727	18.47	573	14.61	1527	38.85
Cyprus	41	5.48	4	0.55	98	13.42	450	61.64
Czech post-MONICA	58	2.27	52	2.03	100	3.97	715	27.95
DCH	135	NA*	66	NA*	105	3.84	1633	59.69
EAS	144	16.53	73	8.38	25	2.86	452	51.78
ELSA	184	3.38	155	2.84	360	6.61	3352	61.50
EPIC InterAct	NA	NA	NA	NA	3535	NA*	NA	NA
EPIC Netherlands	1221	NA*	443	NA*	369	8.26	1906	36.79
EPIC Norfolk	613	NA*	300	NA*	449	2.22	8218	40.77
EPIC Potsdam	224	NA*	30	NA*	106	4.70	812	36.04
EPIC Turin	32	0.74	9	0.21	63	1.46	1920	42.42
FHS	28	2.77	37	3.42	110	14.29	64	53.78
HAPIEE Czech	401	6.12	293	4.47	350	5.26	3630	54.49
HAPIEE Lithuania	652	9.40	311	4.48	392	5.68	3824	55.35
HAPIEE Poland	425	7.42	131	2.29	421	7.37	2684	47.06
HAPIEE Russia	630	8.89	461	6.51	256	3.61	4038	57.03
HIMS	540	13.47	224	5.59	339	8.09	3410	81.36

Study	Coronary heart disease		Stroke (combined sub-types)		Diabetes		Hypertension	
	N	Proportion (%)	N	Proportion (%)	N	Proportion (%)	N	Proportion (%)
HPFS	424	NA*	NA	NA	69	5.46	404	31.96
IMPROVE Groeningen	59	14.05	13	3.09	234	56.52	277	66.27
IMPROVE Kuopio 1	38	7.90	7	1.46	84	17.57	295	61.46
IMPROVE Kuopio 2	67	14.77	11	2.50	201	46.10	364	82.73
IMPROVE Milan	16	3.11	3	0.58	65	11.95	205	39.88
IMPROVE Paris	29	6.65	7	1.61	107	25.12	99	22.71
IMPROVE Perugia	47	10.13	8	1.72	69	15.00	231	49.78
IMPROVE Stockholm	38	7.92	13	2.71	97	20.77	367	76.46
Inter99	45	0.74	59	0.97	364	6.03	2341	36.97
ISGS-SWISS	NA	NA	794	NA *	NA	NA	NA	NA
Izhevsk	NA	NA	NA	NA	11	1.70	383	58.65
MDC	57	2.94	47	2.43	35	1.81	4	0.21
MESA	47	2.05	32	1.40	220	9.59	483	21.08
MRC 1958BC	NA	NA	NA	NA	78	3.10	609	23.64
MRC NSHD	42	1.56	20	0.74	77	2.86	1194	44.92
NHANES III	239	10.01	NA	NA	239	10.01	716	29.98
NHS	442	NA*	NA	NA	120	9.08	466	35.25
NORDIL	23	1.20	26	1.35	131	6.82	1921	100.00
NPHSII	179	6.73	84	3.16	67	2.52	1362	51.22
Portuguese Stroke Study	NA	NA	569	NA*	NA	NA	NA	NA
PREVEND	451	5.95	197	2.59	274	3.56	2111	27.31
PROCARDIS	3116	NA *	NA	NA	NA	NA	NA	NA
PROSPER	731	13.28	617	11.21	592	10.76	4326	78.60
Rotterdam	1094	18.84	835	14.33	608	10.44	2672	47.26
SMART	NA	NA	NA	NA	NA	NA	NA	NA
TPT	36	1.13	NA	NA	NA	NA	1604	50.52
UCP	622	NA *	NA	NA	323	20.15	NA	NA
ULSAM	85	18.76	92	20.31	48	10.60	331	73.07

Study	Coronary heart disease		Stroke (combined sub-types)		Diabetes		Hypertension	
	N	Proportion (%)	N	Proportion (%)	N	Proportion (%)	N	Proportion (%)
Whitehall II	212	4.22	116	2.31	183	3.64	765	15.21
WHI	2943	NA*	2126	NA*	604	NA*	2736	34.71

Footnote: NA: not available; * for case control, nested case-cohort or nested case-control studies, the proportion was not estimated

Table S6. Lifestyle characteristics of studies included in the collaboration

Study	Ever smoker	Smoking frequency (cigs/day)		ln Cotinine (nmol/l)		Pack years		Physical activity (hours/week)		Education (years)	
	Proportion (%)	N	mean (SD)	N	mean (SD)	N	mean (SD)	N	mean (SD)	N	mean (SD)
ALSPAC	38.96	522	15.21(8.72)	NA	NA	919	16.43(14.00)	NA	NA	NA	NA
ARIC	59.75	1950	20.23(12.18)	NA	NA	9382	17.02(21.78)	NA	NA	NA	NA
BRHS	67.45	399	13.87(9.09)	3666	-0.41(2.9)	NA	NA	NA	NA	3325	11.35(2.79)
BWHHS	43.90	353	12.25(6.59)	3352	0.61 (2.61)	867	18.95(16.98)	3275	2.74(5.55)	3183	11.21(2.60)
CaPS	81.59	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
CARDIA	23.70	582	14.92(10.72)	NA	NA	580	6.19(6.77)	NA	NA	1433	14.76(2.29)
CCHS	77.49	9010	8.13(10.54)	NA	NA	NA	NA	8992	2.26(0.71)	9011	9.16(2.15)
CFS	57.50	NA	NA	NA	NA	127	16.83(22.12)	NA	NA	NA	NA
CGPS	58.03	NA	NA	NA	NA	NA	NA	57041	2.47(0.72)	NA	NA
CHS	54.18	NA	NA	NA	NA	3830	18.83(27.59)	NA	NA	3927	14(4.58)
Cyprus	38.63	282	24.21(17.55)	NA	NA	730	13.56(27.97)	729	2.67(1.81)	NA	NA
Czech post-MONICA	47.15	1164	14.23(9.44)	NA	NA	1206	16.89(15.03)	NA	NA	2555	12.53(2.66)
DCH	72.54	NA	NA	NA	NA	NA	NA	2710	1.24(2.1)	NA	NA
EAS	60.58	518	15.96(8.02)	NA	NA	502	25.08(18.05)	873	0.59(1.84)	NA	NA
ELSA	70.28	5403	2.67(7.00)	NA	NA	5395	5.37(14.34)	NA	NA	NA	NA
EPIC InterAct	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
EPIC Netherlands	63.85	1487	15.44(9.03)	NA	NA	1471	25.54(16.73)	5186	2.81(1.03)	NA	NA
EPIC Norfolk	54.43	2048	14.33(8.21)	NA	NA	20185	9.88(15.35)	20195	2.3(1.09)	NA	NA
EPIC Potsdam	54.68	2253	3.12(7.24)	NA	NA	NA	NA	2253	0.99(1.71)	NA	NA
EPIC Turin	59.70	1049	13.41(9.07)	NA	NA	1048	19.27(14.81)	NA	NA	4305	11.97(4.53)
FHS	61.15	NA	NA	NA	NA	112	13.16(19.05)	NA	NA	768	14.35(2.77)
HAPIEE Czech	55.32	4043	12.21(9.81)	NA	NA	3462	20.97(16.88)	6496	4.32(5.32)	NA	NA
HAPIEE Lithuania	37.30	2487	15(9.81)	NA	NA	2479	22.82(18.36)	6894	3.25(5.91)	NA	NA

Study	Ever smoker	Smoking frequency (cigs/day)		ln Cotinine (nmol/l)		Pack years		Physical activity (hours/week)		Education (years)	
	Proportion (%)	N	mean (SD)	N	mean (SD)	N	mean (SD)	N	mean (SD)	N	mean (SD)
HAPIEE Poland	58.43	3970	15.12(12.40)	NA	NA	3257	27.45(20.38)	5442	5.35(5.96)	NA	NA
HAPIEE Russia	40.00	2793	16.06(9.56)	NA	NA	2792	28.08(20.44)	7076	2.41(5.86)	NA	NA
HPFS	41.61	111	2.00(0.97)	NA	NA	1232	15.18(20.37)	1264	3.49(5.01)	NA	NA
HIMS	66.45	4176	14.56(17.11)	NA	NA	2740	37.75(34.10)	4186	5.52(5.63)	NA	NA
IMPROVE Groeningen	69.83	292	14.61(8.46)	NA	NA	419	15.38(17.50)	NA	NA	NA	NA
IMPROVE Kuopio 1	53.01	248	14.18(8.52)	NA	NA	462	9.79(16.02)	NA	NA	NA	NA
IMPROVE Kuopio 2	47.05	195	15.41(10.12)	NA	NA	428	8.93(14.58)	NA	NA	NA	NA
IMPROVE Milan	51.75	262	17.53(13.43)	NA	NA	510	13.91(23.08)	NA	NA	NA	NA
IMPROVE Paris	47.25	203	16.31(10.29)	NA	NA	431	9.61(15.39)	NA	NA	NA	NA
IMPROVE Perugia	40.09	186	16.38(7.10)	NA	NA	464	8.51(15.08)	NA	NA	NA	NA
IMPROVE Stockholm	55.83	249	14.1(7.68)	NA	NA	461	11.25(15.18)	NA	NA	NA	NA
Inter99	64.34	2207	16.81(8.65)	NA	NA	2418	15.14(13.80)	5889	4.86(2.70)	6081	12.16(3.17)
ISGS-SWISS	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Izhevsk	81.60	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
MDC	66.75	522	13.83(8.15)	NA	NA	516	24.31 (16.65)	NA	NA	NA	NA
MESA	55.88	NA	NA	NA	NA	2264	15.35(28.33)	NA	NA	NA	NA
MRC 1958BC	53.64	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
MRC NSHD	71.28	597	16.88 (9.76)	NA	NA	2169	11.42(14.52)	NA	NA	NA	NA
NHANES III	50.00	494	21.10 12.30)	2360	1.58 (3.36)	488	16(19.80)	2383	5.50(6.10)	2382	12.40(2.90)
NHS	64.52	346	1.95(0.90)	NA	NA	1304	18.8(22.67)	1322	1.87(2.89)	NA	NA
NORDIL	25.82	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
NPHSII	68.45	1883	18.04(14.38)	NA	NA	1665	29.65(23.35)	NA	NA	NA	NA
Portuguese Stroke Study	48.30	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
PREVEND	71.37	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
PROCARDIS	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

Study	Ever smoker	Smoking frequency (cigs/day)		ln Cotinine (nmol/l)		Pack years		Physical activity (hours/week)		Education (years)	
	Proportion (%)	N	mean (SD)	N	mean (SD)	N	mean (SD)	N	mean (SD)	N	mean (SD)
PROSPER	26.84	NA	NA	NA	NA	NA	NA	NA	NA	5504	15.12(2.03)
Rotterdam	64.62	1198	14.56(8.68)	NA	NA	3328	28.03(24.34)	NA	NA	NA	NA
SMART	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
TPT	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
UCP	69.36	690	18.15(11.95)	NA	NA	660	31.85(26.55)	NA	NA	NA	NA
ULSAM	66.67	NA	NA	NA	NA	300	39.92(35.54)	NA	NA	NA	NA
Whitehall II	41.63	709	14.88(10.21)	NA	NA	655	19.62(14.67)	4899	3.01(3.38)	3700	14.46(3.59)
WHI	49.94	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

Footnote: NA: not available

Table S7. Cardiovascular traits characteristics of the studies included in the collaboration (1)

Study	SBP (mmHg)		HDL-C (mmol/l)		non-HDL-C (mmol/l)		ln triglycerides (mmol/l)		Apolipoprotein A (g/l)		Apolipoprotein B (g/l)		ln lipoprotein(a) (mg/dl)		Fasting glucose (mmol/l)	
	N	mean (SD)	N	mean (SD)	N	mean (SD)	N	mean (SD)	N	mean (SD)	N	mean (SD)	N	mean (SD)	N	mean (SD)
ALSPAC	2496	117.70(12.14)	2395	1.47(0.39)	2395	3.42(0.89)	2395	-0.08 (0.44)	NA	NA	NA	NA	NA	NA	NA	NA
ARIC	9554	118.35(17.00)	9540	1.31(0.43)	9538	4.24(1.12)	9540	0.29(0.52)	NA	NA	NA	NA	NA	NA	7717	5.91(1.69)
BRHS	3827	149.29(24.22)	3763	1.32(0.34)	3763	4.67(1.08)	3788	0.49(0.48)	NA	NA	NA	NA	NA	NA	3823	5.55(1.24)
BWHHS	3401	147.03(25.12)	3367	1.66(0.45)	3367	4.98(1.25)	3373	0.51(0.46)	NA	NA	NA	NA	NA	NA	3357	6.06(1.64)
CaPS	1076	145.73(22.4)	1067	1.39(0.38)	1067	4.50(1.11)	1059	0.38(0.57)	1036	1.26(0.20)	1033	0.96(0.20)	NA	NA	NA	NA
CARDIA	1433	109.26(10.81)	1427	1.34(0.33)	1427	3.22(0.86)	1426	-0.27 (0.51)	1425	1.36(0.19)	1425	0.91(0.23)	1321	1.86(1.33)	1321	4.74(0.97)
CCHS	9072	138.89(22.52)	9066	1.58(0.50)	9066	4.58(1.34)	9053	0.47(0.54)	NA	NA	NA	NA	NA	NA	NA	NA
CFS	134	128.92(17.05)	40	1.06(0.34)	40	3.49(1.09)	40	0.48(0.48)	NA	NA	NA	NA	NA	NA	40	6.00(2.24)
CGPS	56948	140.31(21.32)	57012	1.64(0.52)	57012	4.03(1.11)	57010	0.37(0.55)	NA	NA	NA	NA	NA	NA	NA	NA
CHS	3930	135.48(21.45)	3922	1.38(0.40)	3922	4.09(1.00)	3927	0.38(0.43)	NA	NA	NA	NA	3921	1.09(1.24)	3922	6.04(1.82)
Cyprus	713	138.97(17.06)	711	1.30(0.32)	711	4.57(1.02)	711	0.41(0.48)	711	1.44(0.24)	710	1.20(0.24)	688	2.01(0.92)	710	5.77(1.59)
Czech post-MONICA	2526	127.38(17.14)	2518	1.39(0.36)	2518	4.27(1.22)	2523	0.39(0.56)	NA	NA	NA	NA	NA	NA	2548	5.30(1.18)
DCH	2735	143.47(21.08)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
EAS	872	143.24(23.63)	867	1.45(0.38)	867	5.63(1.31)	872	0.32(0.45)	NA	NA	NA	NA	568	-1.09 (1.40)	871	5.80(1.49)
ELSA	4027	140.13(19.22)	2019	1.45(0.43)	2019	4.52(1.14)	5419	0.45(0.51)	NA	NA	NA	NA	NA	NA	3235	5.02(0.93)
EPIC InterAct	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
EPIC Netherlands	5164	133.07(21.17)	3580	1.40(0.41)	3060	4.23(1.25)	4321	0.44(0.56)	NA	NA	NA	NA	NA	NA	3456	5.41(2.21)
EPIC Norfolk	20158	135.46(18.19)	18958	1.42(0.43)	18958	4.73(1.17)	19635	0.46(0.53)	15602	1.55(0.33)	15520	0.97(0.25)	15782	2.57(0.97)	NA	NA
EPIC Potsdam	2253	130.12(18.04)	2253	1.35(0.37)	2253	3.19(0.91)	2253	0.19(0.59)	NA	NA	NA	NA	NA	NA	325	5.56(1.54)
EPIC Turin	4526	132.39(15.74)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
FHS	119	135.61(20.40)	756	1.32(0.40)	756	3.80(1.09)	757	1.05(0.67)	704	1.44(0.30)	704	1.00(0.25)	506	1.93(1.37)	740	5.60(0.60)
HAPIEE Czech	6662	139.14(19.66)	6502	1.39(0.39)	6501	4.33(1.07)	6522	0.49(0.53)	NA	NA	NA	NA	NA	NA	901	5.77(1.63)
HAPIEE Lithuania	6909	139.65(21.65)	6776	1.49(0.38)	6776	4.46(1.16)	6894	0.26(0.48)	NA	NA	NA	NA	NA	NA	6764	5.83(1.25)

Study	SBP (mmHg)		HDL-C (mmol/l)		non-HDL-C (mmol/l)		ln triglycerides (mmol/l)		Apolipoprotein A (g/l)		Apolipoprotein B (g/l)		ln lipoprotein(a) (mg/dl)		Fasting glucose (mmol/l)	
	N	mean (SD)	N	mean (SD)	N	mean (SD)	N	mean (SD)	N	mean (SD)	N	mean (SD)	N	mean (SD)	N	mean (SD)
HAPIEE Poland	5704	137.51(20.87)	5724	1.44(0.38)	5724	4.4(1.06)	5723	0.37(0.48)	NA	NA	NA	NA	NA	NA	5717	5.35(1.38)
HAPIEE Russia	7080	143.1(25.05)	7081	1.54(0.41)	7081	4.85(1.29)	7079	0.34(0.44)	NA	NA	NA	NA	NA	NA	1045	5.97(1.97)
HIMS	4191	155.84(20.42)	3835	1.39(0.36)	3835	3.51(0.92)	3834	0.17(0.51)	NA	NA	NA	NA	NA	NA	3835	5.71(1.45)
HPFS	NA	NA	1264	1.16(0.32)	1264	4.16(0.96)	1264	0.37(0.55)	NA	NA	1264	0.93(0.22)	750	-0.76 (1.28)	NA	NA
IMPROVE Groeningen	418	147.08(18.14)	419	1.12(0.32)	419	3.97(1.03)	419	0.47(0.55)	NA	NA	NA	NA	NA	NA	417	6.52(2.31)
IMPROVE Kuopio 1	480	144.87(17.58)	479	1.30(0.34)	479	3.75(0.92)	479	0.15(0.48)	NA	NA	NA	NA	NA	NA	480	5.85(1.06)
IMPROVE Kuopio 2	440	153.10(17.35)	440	1.27(0.37)	440	4.03(1.04)	440	0.33(0.55)	NA	NA	NA	NA	NA	NA	439	7.08(2.12)
IMPROVE Milan	514	131.49(14.38)	512	1.21(0.34)	512	4.68(0.98)	512	0.34(0.49)	NA	NA	NA	NA	NA	NA	514	5.41(0.99)
IMPROVE Paris	436	128.17(14.35)	436	1.35(0.40)	436	4.31(1.16)	436	0.36(0.60)	NA	NA	NA	NA	NA	NA	436	5.42(1.18)
IMPROVE Perugia	464	139.48(13.43)	464	1.29(0.33)	464	4.74(1.04)	464	0.35(0.53)	NA	NA	NA	NA	NA	NA	464	5.26(1.23)
IMPROVE Stockholm	480	149.45(18.57)	480	1.28(0.38)	480	4.16(1.00)	480	0.13(0.47)	NA	NA	NA	NA	NA	NA	480	6.03(1.45)
Inter99	6331	130.20(17.50)	6328	1.43(0.40)	6327	4.09(1.12)	6328	0.12(0.54)	NA	NA	NA	NA	NA	NA	6326	5.60(1.13)
ISGS-SWISS	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Izhevsk	652	144.86(22.39)	623	1.43(0.45)	623	4.02(1.02)	611	0.28(0.52)	621	1.47(0.31)	621	0.9(0.26)	NA	NA	NA	NA
MDC	1937	115.70(6.15)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
MESA	2291	123.53(20.68)	2286	1.35(0.41)	2286	3.71(0.93)	2288	0.26(0.54)	NA	NA	NA	NA	NA	NA	2288	5.04(1.23)
MRC 1958BC	2576	126.70(16.82)	2544	1.56(0.40)	2544	4.32(1.10)	2543	0.54(0.60)	NA	NA	NA	NA	NA	NA	NA	NA
MRC NSHD	2658	136.11(19.96)	2333	1.67(0.54)	2333	4.36(1.13)	2506	0.58(0.58)	NA	NA	NA	NA	NA	NA	NA	NA
NHANES III	2383	126.80(20.2)	2364	1.3(0.40)	2362	4.10(1.20)	2379	0.37(0.57)	NA	NA	NA	NA	NA	NA	1108	5.70(1.70)
NHS	NA	NA	1322	1.48(0.43)	1321	4.44(1.07)	1227	0.23(0.51)	183	1.73(.33)	1322	1.09(0.32)	683	-0.97 (1.27)	NA	NA
NORDIL	1921	177.23(14.53)	1820	1.37(0.46)	1819	4.96(1.21)	1889	0.47(0.51)	NA	NA	NA	NA	NA	NA	1892	5.26(1.54)
NPHS II	2658	138.54(19.08)	1771	0.84(0.25)	1759	4.9(1.04)	2641	0.59(0.53)	2266	1.63(0.32)	2266	0.9(0.26)	2206	-1.07 (1.36)	NA	NA
Portuguese Stroke Study	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
PREVEND	7726	129.20(20.31)	7607	1.32(0.40)	7575	4.33(1.21)	7280	0.19(0.52)	7405	1.39(0.30)	7406	1.03(0.31)	7405	-2.76 (1.02)	6946	4.9(1.1)

Study	SBP (mmHg)		HDL-C (mmol/l)		non-HDL-C (mmol/l)		ln triglycerides (mmol/l)		Apolipoprotein A (g/l)		Apolipoprotein B (g/l)		ln lipoprotein(a) (mg/dl)		Fasting glucose (mmol/l)	
	N	mean (SD)	N	mean (SD)	N	mean (SD)	N	mean (SD)	N	mean (SD)	N	mean (SD)	N	mean (SD)	N	mean (SD)
PROCARDIS	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
PROSPER	5504	154.62(21.87)	5504	1.28(0.35)	5504	4.41(0.90)	5504	0.35(0.41)	5444	1.32(0.24)	5444	1.15(0.22)	5444	2.61(1.25)	5482	5.47(1.45)
Rotterdam	5654	139.32(22.34)	5738	1.34(0.36)	5737	5.26(1.23)	3355	0.33(0.43)	NA	NA	NA	NA	NA	NA	3400	5.96(1.57)
SMART	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
TPT	3175	138.49(17.88)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
UCP	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
ULSAM	452	149.18(18.88)	452	1.29(0.34)	452	4.49(0.95)	453	0.24(0.46)	313	1.27(0.23)	315	1.03(0.22)	314	-0.49 (1.18)	453	5.73(1.36)
Whitehall II	5022	122.23(13.93)	826	1.47(0.40)	826	4.80(1.18)	857	0.56(0.56)	3834	1.55(0.26)	3834	1.02(0.25)	4737	-0.3(0.89)	4541	5.22(0.59)
WHI	7877	132.96(18.69)	4248	1.42(0.40)	4175	4.54(1.08)	3314	0.50(0.48)	NA	NA	NA	NA	NA	NA	NA	NA

Footnote: NA: not available

Table S8. Cardiovascular traits characteristics of studies included in the collaboration (2)

Study	ln Fibrinogen (g/l)		von Willebrand factor (IU/dl)		ln CRP (mg/l)		ln IL6 (pg/ml)		BMI (kg/m^2)		Waist circumference (cm)		ln CIMT (mm)		ln BNP (ng/l)	
	N	mean (SD)	N	mean (SD)	N	mean (SD)	N	mean (SD)	N	mean (SD)	N	mean (SD)	N	mean (SD)	N	mean (SD)
ALSPAC	NA	NA	NA	NA	2395	0.10 (1.13)	NA	NA	2554	26.54 (5.21)	2554	84.37 (12.19)	2543	-0.59 (0.11)	NA	NA
ARIC	9464	1.07 (0.20)	NA	NA	7559	0.81 (1.08)	297	0.69 (0.68)	9549	26.98 (4.85)	9547	96.11 (13.33)	NA	NA	NA	NA
BRHS	3835	1.16 (0.22)	3837	140.08 (46.30)	3811	0.57 (1.11)	3807	0.90 (0.67)	3824	26.90 (3.70)	3818	97.17 (10.44)	NA	NA	NA	NA
BWHHS	3341	1.22 (0.20)	3348	148.26 (47.55)	3244	0.62 (1.11)	3341	0.85 (0.69)	3383	27.56 (4.94)	3368	86.17 (12.09)	NA	NA	1200	5.07 (0.95)
CaPS	1092	1.30 (0.22)	NA	NA	741	0.51 (1.00)	NA	NA	1084	26.30 (3.47)	1077	94.13 (10.31)	NA	NA	NA	NA
CARDIA	675	0.69 (0.22)	675	90.77 (33.84)	1308	-0.03 (1.20)	224	0.01 (0.65)	1427	23.63 (3.99)	1426	76.96 (10.45)	84	-0.68 (0.18)	NA	NA
CCHS	8818	1.09 (0.27)	NA	NA	8251	0.79 (0.78)	NA	NA	9051	25.62 (4.34)	NA	NA	NA	NA	NA	NA
CFS	37	1.19 (0.22)	NA	NA	40	0.79 (0.94)	40	1.05 (0.65)	134	32.35 (8.04)	45	103.36 (19.48)	NA	NA	NA	NA
CGPS	56859	1.32 (0.24)	NA	NA	NA	NA	NA	NA	56742	26.15 (4.29)	NA	NA	NA	NA	NA	NA
CHS	3902	1.14 (0.20)	NA	NA	3908	0.63 (1.01)	3620	0.57 (0.62)	3924	26.38 (4.50)	3907	93.81 (12.83)	3918	-0.18 (0.22)	NA	NA
Cyprus	704	0.97 (0.20)	NA	NA	697	0.79 (1.27)	216	0.62 (1.09)	716	28.08 (4.59)	65	97.12 (19.91)	730	-0.33 (0.21)	NA	NA
Czech post-MONICA	NA	NA	NA	NA	2346	0.00 (1.01)	NA	NA	2524	27.20 (4.71)	2525	89.67 (13.03)	NA	NA	NA	NA
DCH	NA	NA	NA	NA	NA	NA	NA	NA	2736	26.53 (4.00)	2736	91.67 (12.70)	NA	NA	NA	NA
EAS	854	0.96 (0.25)	790	111.74 (43.70)	640	0.66 (1.09)	619	0.80 (0.74)	873	25.53 (3.84)	NA	NA	825	-0.33 (0.32)	NA	NA
ELSA	1823	1.01 (0.24)	NA	NA	5416	0.72 (1.11)	NA	NA	5144	27.46 (4.37)	4415	92.68 (12.71)	NA	NA	NA	NA
EPIC InterAct	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
EPIC Netherlands	NA	NA	NA	NA	4338	0.83 (1.69)	NA	NA	5184	26.77 (4.45)	5180	88.47 (12.49)	NA	NA	NA	NA
EPIC Norfolk	18654	1.05 (0.28)	NA	NA	15709	0.49 (1.06)	NA	NA	20169	26.30 (3.81)	20182	88.42 (12.32)	NA	NA	NA	NA
EPIC-Potsdam	NA	NA	NA	NA	2253	-0.25 (1.39)	NA	NA	2249	26.19 (4.29)	2252	86.41 (12.96)	NA	NA	NA	NA
EPIC Turin	NA	NA	NA	NA	NA	NA	NA	NA	4467	25.85 (3.59)	4296	89.02 (11.55)	NA	NA	NA	NA
FHS	308	1.26 (0.21)	689	131.77 (47.23)	312	0.41 (1.26)	693	1.11 (0.72)	312	27.72 (5.73)	728	90.04 (14.55)	671	-0.53 (0.26)	NA	NA
HAPIEE Czech	NA	NA	NA	NA	6540	0.30 (1.03)	NA	NA	6673	28.20 (4.56)	6671	93.32 (12.73)	NA	NA	NA	NA

Study	ln Fibrinogen (g/l)		von Willebrand factor (IU/dl)		ln CRP (mg/l)		ln IL6 (pg/ml)		BMI (kg/m^2)		Waist circumference (cm)		ln CIMT (mm)		ln BNP (ng/l)	
	N	mean (SD)	N	mean (SD)	N	mean (SD)	N	mean (SD)	N	mean (SD)	N	mean (SD)	N	mean (SD)	N	mean (SD)
HAPIEE Lithuania	NA	NA	NA	NA	926	0.42 (1.11)	NA	NA	6930	29.36 (5.29)	6903	92.61 (13.49)	NA	NA	NA	NA
HAPIEE Poland	NA	NA	NA	NA	567	0.44 (1.06)	NA	NA	5720	28.15 (4.50)	5726	92.45 (12.29)	NA	NA	NA	NA
HAPIEE Russia	NA	NA	NA	NA	1045	0.49 (1.20)	NA	NA	7082	28.61 (5.45)	7080	92.89 (12.84)	NA	NA	NA	NA
HIMS	NA	NA	NA	NA	3834	0.70 (1.04)	NA	NA	4188	26.77 (3.41)	4191	98.65 (9.81)	NA	NA	NA	NA
HPFS	756	1.37 (0.20)	NA	NA	1262	0.16 (1.11)	755	0.66 (0.94)	1264	25.78 (3.31)	1170	98.29 (10.01)	NA	NA	NA	NA
IMPROVE Groeningen	NA	NA	NA	NA	420	0.88 (1.12)	NA	NA	420	29.40 (4.76)	415	101.71 (12.28)	421	-0.13 (0.24)	NA	NA
IMPROVE Kuopio 1	NA	NA	NA	NA	480	0.14 (1.29)	NA	NA	481	27.72 (4.02)	481	93.19 (11.06)	480	-0.07 (0.21)	NA	NA
IMPROVE Kuopio 2	NA	NA	NA	NA	440	0.32 (1.25)	NA	NA	440	29.12 (4.62)	439	99.17 (13.43)	439	-0.07 (0.20)	NA	NA
IMPROVE Milan	NA	NA	NA	NA	514	0.35 (1.17)	NA	NA	514	25.24 (3.28)	512	88.07 (10.49)	514	-0.15 (0.20)	NA	NA
IMPROVE Paris	NA	NA	NA	NA	436	0.27 (1.26)	NA	NA	436	26.34 (3.83)	435	93.08 (12.79)	436	-0.22 (0.18)	NA	NA
IMPROVE Perugia	NA	NA	NA	NA	464	0.66 (1.07)	NA	NA	464	26.27 (3.51)	464	88.34 (10.30)	464	-0.24 (0.18)	NA	NA
IMPROVE Stockholm	NA	NA	NA	NA	480	0.43 (1.27)	NA	NA	480	26.82 (4.13)	480	95.27 (11.77)	480	-0.09 (0.19)	NA	NA
Inter99	718	0.55 (0.72)	NA	NA	5629	-0.12 (1.29)	621	1.08 (1.02)	6328	26.31 (4.62)	6318	86.55 (13.34)	NA	NA	NA	NA
ISGS-SWISS	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Izhevsk	NA	NA	NA	NA	NA	NA	NA	NA	649	26.71 (4.97)	653	94.79 (11.79)	NA	NA	NA	NA
MDC	NA	NA	NA	NA	NA	BA	NA	NA	1936	24.39 (3.31)	1936	81.24 (14.46)	NA	NA	NA	NA
MESA	2283	1.19 (0.20)	415	134.55 (54.34)	2284	0.58 (1.15)	2251	0.15 (0.66)	2293	27.75 (5.06)	2293	97.97 (14.53)	2269	-0.34 (0.26)	NA	NA
MRC 1958BC	2512	1.07 (0.20)	2513	124.32 (41.74)	2513	0.02 (1.20)	NA	NA	2585	27.26 (4.82)	2580	92.00 (13.58)	NA	NA	NA	NA
MRC NSHD	NA	NA	NA	NA	NA	NA	NA	NA	2671	27.34 (4.65)	2682	91.62 (13.06)	NA	NA	NA	NA
NHANES III	NA	NA	NA	NA	NA	NA	NA	NA	2388	26.60 (5.60)	2300	92.90 (14.70)	NA	NA	NA	NA
NHS	707	1.23 (0.27)	NA	NA	1322	0.72 (1.15)	675	0.63 (0.68)	1321	25.66 (4.75)	942	80.06 (11.10)	NA	NA	NA	NA
NORDIL	NA	NA	NA	NA	NA	NA	NA	NA	1883	28.27 (4.57)	NA	NA	NA	NA	NA	NA

Study	ln Fibrinogen (g/l)		von Willebrand factor (IU/dl)		ln CRP (mg/l)		ln IL6 (pg/ml)		BMI (kg/m^2)		Waist circumference (cm)		ln CIMT (mm)		ln BNP (ng/l)	
	N	mean (SD)	N	mean (SD)	N	mean (SD)	N	mean (SD)	N	mean (SD)	N	mean (SD)	N	mean (SD)	N	mean (SD)
NPHSII	2646	1.00 (0.19)	170	110.46 (34.61)	2205	0.92 (1.00)	NA	NA	2656	26.45 (3.5)	NA	NA	NA	NA	NA	NA
Portuguese Stroke Study	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
PREVEND	NA	NA	NA	NA	7327	0.25 (1.13)	NA	NA	7653	26.08 (4.21)	7654	88.12 (9.58)	712	-0.28 (0.23)	NA	NA
PROCARDIS	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
PROSPER	5357	1.26 (0.21)	5327	140.79 (45.90)	5400	1.13 (1.12)	5374	0.98 (0.66)	5504	26.84 (4.19)	NA	NA	NA	NA	NA	NA
Rotterdam	2354	0.99 (0.24)	3380	137.20 (63.63)	5458	0.62 (1.04)	NA	NA	5635	26.29 (3.68)	5341	90.62 (11.12)	4745	0.00 (0.19)	3355	4.74 (1.06)
SMART	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	7917	-0.17 (0.28)	2700	2.47 (0.98)
TPT	3109	1.09 (0.19)	NA	NA	NA	NA	NA	NA	3162	27.47 (3.56)	NA	NA	NA	NA	NA	NA
UCP	NA	NA	NA	NA	NA	NA	NA	NA	1480	27.14 (4.15)	NA	NA	NA	NA	NA	NA
ULSAM	319	1.27 (0.27)	NA	NA	435	0.64 (1.01)	405	1.39 (0.84)	452	26.02 (3.24)	445	94.59 (9.21)	NA	NA	444	4.83 (1.15)
Whitehall II	1456	0.98 (0.20)	4306	104.80 (38.84)	4488	-0.16 (1.16)	4466	0.37 (0.59)	5022	24.35 (3.30)	4691	84.78 (11.35)	3249	-0.26 (0.19)	NA	NA
WHI	2453	1.08 (0.25)	NA	NA	4681	0.69 (1.36)	3546	0.81 (0.74)	7814	28.35 (6.26)	NA	NA	NA	NA	NA	NA

Footnote: NA: not available

Table S9. Meta-analysis pooled estimates of the association between *ADH1B* rs1229984 (A-allele carriers vs. GG-subjects) and cardiovascular biomarkers, irrespective of alcohol intake, limited to traits not showing association at a nominal P value equal to 0.05.

Trait (units)	Studies/Individuals	Mean difference (95%CI)	P-value	I^2, %
DBP (mmHg)	48/227550	-0.08 (-0.25, 0.10)	0.401	23
Ln Fibrinogen (g/l) †	27/136647	-0.07 (-0.60,0.47)	0.808	41
Glucose (fasting, mmol/l)	35/88388	-0.03 (-0.06, 0.00)	0.064	36
Ln Lipoprotein(a) (mg/dl) †	14/46287	0.75 (-3.11,4.76)	0.709	38
Apolipoprotein B (g/l)	13/41865	-0.00 (-0.01, 0.01)	0.357	51
Apoliporotein A-1 (g/l)	12/39544	0.00 (-0.01, 0.02)	0.57	48
Ln cIMT (mm) †	18/30897	-0.09 (-0.95,0.77)	0.839	10
Von Willebrand factor (IU/dl)	11/25450	0.07 (-2.43, 2.58)	0.956	41
Sokolow-Lyon (mm)	4/21460	22.03 (-19.86, 63.93)	0.303	0
QRS Voltage Sum (mm)	4/21445	90.62 (-106.19, 287.42)	0.367	47
QRS Voltage Product (mm)	4/21440	8.13 (-17.07, 33.32)	0.527	61
Cornell Product (µV.S)	4/21408	-2.08 (-5.73, 1.57)	0.264	51
Ln BNP (ng/l) †	8/20794	-3.02 (-9.79,4.28)	0.407	54
Factor VII (U/ml)	10/20509	0.30 (-1.34, 1.93)	0.721	0

Footnote: † for log(e) transformed traits, the percentage difference in the geometric mean is reported rather than the mean difference. BNP: NT-pro brain derived natriuretic peptide; cIMT: carotid intima medial thickness; DBP: diastolic blood pressure;

Table S10. Meta-analysis pooled estimates of the association between *ADH1B* rs1229984 (A-allele carriers vs. non-carriers) and CHD in all studies and in studies with ≥1000 CHD events

Group	Studies, Cases/Total	Odds ratio (95%CI) of CHD (rs1229984 A-allele carriers vs. non-carriers)
All studies	46, 20259/168731	0.90 (0.84, 0.96)
Studies with ≥1000 CHD events	4, 8374/23135	0.81 (0.72, 0.91)

Table S11. Linkage disequilibrium between rs1229984 and SNPs on chromosome 4 that are associated with cardiometabolic traits from GWAs and gene-centric array analyses

SNP	Platform	Primary phenotype	Base pair position	Distance from rs1229984 (bp)	R^2 with rs1229984
rs13107325	GWAs	Systolic & Diastolic BP, HDL-C	103188709	2949390	NA
rs1458038	GWAs	Systolic BP	81164723	-19074596	NA
rs16998073	GWAs	Diastolic BP	81184341	-19054978	NA
rs871606	GWAs	BP	54799245	-45440074	NA
rs442177	GWAs	Triglycerides	88030261	-12209058	NA
rs1878406	GWAs	Carotid intima media thickness	148393664	48154345	NA
rs2200733	GWAs	Stroke (ischemic)	111710169	11470850	$1.19x10^{-3}$
rs4688985	Gene centric	Type-2 diabetes	6285715	-93953604	$1.88x10^{-3}$
rs4689388	GWAs	Type-2 diabetes and other traits	6270056	-93969263	$3.87x10^{-5}$
rs7659604	GWAs	Type-2 diabetes	122665514	22426195	$2.46x10^{-5}$

Footnotes The analysis was conducted in Whitehall II, restricted to Europeans using PLINK. NA: not available as SNP on Metabochip and not IBC 50K CardioChip.[6] BP: blood pressure. For those SNPs with R^2 annotated as "NA", the distance from the rs1229984 makes it unlikely that LD value between the SNP with rs1229984 would be high. GWAs: genome wide association study

Table S12. Meta-analysis pooled linear and quadratic coefficients of the association between alcohol and traits on observational analysis, adjusted for age and gender.

Trait	Number	Linear beta (95%CI)	P-value	Quadratic beta (95%CI)	P-value
BMI	130909	-0.14(-0.16,-0.13)	1.50E-92	0.03(0.03,0.03)	8.60E-54
SBP	129573	-0.10(-0.12,-0.09)	1.10E-51	0.04(0.03,0.04)	5.40E-84
DBP	129557	-0.06(-0.08,-0.05)	6.50E-20	0.03(0.03,0.03)	3.00E-52
ln TG	112496	-0.12(-0.14,-0.11)	1.70E-58	0.03(0.02,0.03)	3.30E-43
HDL-C	109998	0.11(0.09,0.12)	3.00E-48	0.02(0.01,0.02)	8.90E-21
Non-HDL	109910	-0.05(-0.06,-0.03)	1.00E-09	0.01(0.00,0.01)	3.30E-05
Waist circumference	108381	-0.14(-0.15,-0.12)	2.70E-82	0.04(0.03,0.04)	5.60E-79
ln CRP	90131	-0.15(-0.16,-0.13)	4.00E-66	0.04(0.03,0.04)	3.90E-56
Physical activity	88630	0.07(0.05,0.09)	6.60E-16	-0.01(-0.02,-0.01)	9.50E-09
Pack years	69727	-0.16(-0.18,-0.15)	1.40E-69	0.07(0.06,0.07)	7.00E-150
Education	66022	0.25(0.23,0.27)	2.00E-140	-0.04(-0.05,-0.04)	3.70E-63
Glucose	65571	-0.07(-0.09,-0.05)	1.00E-12	0.02(0.01,0.02)	7.10E-11
ln Fibrinogen	64288	-0.12(-0.14,-0.10)	1.00E-29	0.01(0.00,0.01)	5.30E-03
Cigarettes/day	48323	-0.19(-0.21,-0.17)	4.80E-72	0.07(0.06,0.07)	2.00E-127
ln GGT	31588	-0.15(-0.18,-0.13)	9.50E-30	0.09(0.08,0.09)	3.00E-118
ln Lp(a)	29319	0.01(-0.02,0.04)	0.57	-0.01(-0.01,0.00)	0.28
ApoA-1	26153	0.04(0.00,0.07)	0.024	0.04(0.03,0.05)	1.70E-15
ApoB	26146	-0.08(-0.11,-0.04)	1.50E-05	0.02(0.01,0.03)	1.20E-06
lnIL6	23535	-0.20(-0.23,-0.17)	1.40E-31	0.05(0.04,0.06)	2.30E-24
Von Willebrand factor	17983	-0.11(-0.15,-0.07)	2.40E-08	0.02(0.01,0.03)	6.50E-04
Factor VII	17305	-0.05(-0.09,-0.01)	0.016	0.01(0.00,0.03)	0.012
ln CIMT	14797	-0.08(-0.12,-0.04)	4.50E-05	0.02(0.01,0.03)	2.80E-05
ln Cotinine	6960	-0.27(-0.33,-0.21)	8.00E-18	0.09(0.07,0.11)	8.40E-23
ln NT-proBNP	4553	-0.06(-0.14,0.01)	0.092	0.02(-0.00,0.04)	0.056

Footnote: traits were standardized prior to analysis thus beta coefficients represent the difference in standard deviation for each trait

6. References

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